Trisomy 21
detection
software

Basic and Advanced User Guide

SBP Soft 2007 S.L.
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Declaración CE de Conformidad

Vía CERTIFICADO CE DE SISTEMA DE GARANTÍA DE LA CALIDAD TOTAL
de acuerdo con el Anexo IV (excepto punto 4) de la Directiva 98/79/CE por el
Organismo Notificado nº 0318

Fabricante: SBP Soft 2007 S.L.
Dirección: C. Joan Maragall 31, 1ºC, 17002, Girona, Spain

SBP Soft 2007 S.L. declara que el producto, o los productos de la misma versión,

Nombre del Producto: SsdwLab versión 6.1

Descripción: Software para la detección prenatal de la trisomía 21
basado en el método de la verosimilitud y que utiliza la
combinación de la edad materna y un conjunto de marcadores
bioquímicos y/o ecográficos en el primer o segundo trimestre
del embarazo.
Los resultados indican el Riesgo materno de que el feto de su
embarazo esté afecto de una trisomía 21.

a los cuales hace referencia esta declaración cumplen los requisitos de la Directiva
98/79/CE del Consejo de la Unión Europea de 27 de Octubre de 1998 y su
transposición al Real Decreto 1662/2000, de 29 de Septiembre, que incorpora la
Reglamentación Comunitaria sobre Productos Sanitarios para Diagnóstico “in vitro”
para todos aquellos Estados Miembros en los cuales este producto pueda ser puesto
en el mercado.

Girona, a 15/04/2014
SBP Soft 2007 S.L.

Firmado en nombre de la compañía

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Introduction

Presentatio

At the beginning of 1995 the first version, 1.0E, of the SSD software for Down's syndrome screening was released. It was very well received and continues to be used by some gynecologists and prenatal diagnosis units. At the end of 1996, the second version was introduced, for use by clinical analysis laboratories.

Both versions were developed in the DOS environment, specifically with the OPEN ACCESS IV integrated package.

Later, Ssdw 1, 2 and SsdwLab 3 and 4 versions were released for use with Windows operating systems, 3.11 for the first and 95/98/NT4/2000 for the others.

In 2006 the distribution of version 5 of SsdwLab began. It facilitated for the first time the simultaneous use of up to 10 biochemical and / or ultrasound markers, with well-known Gaussian distribution and correlation coefficients, as well as up to 15 dichotomous, whose positive and negative likelihood ratio for trisomy 21 is known, and another 15 markers for trisomy 18. The program estimates the trisomy 21 and 18 (18-13) individual risks for each single marker (combined with maternal age) and for the different combination of markers of any type, defined in the Screening Profiles which can be completely customized and defined by the user. This version has been accredited by the Notified Body 0318 of the European Community after having been verified by the EC.

A wider range of equations has been added to the traditional and highly valued characteristics of previous versions (configuration and personalization facilities, automatic calculation of medians and
correction factors, multi-language printing, data server connection, e-mail reports, control of perinatal results and screening quality, etc.). Specifically, equations for medians and maternal weight correction, new correction factors which can be fully defined and calculated by the user, a greater precision in risk estimation for single pregnancies and for mono and dichorionic twin pregnancies, as well as highly effective procedures for the control of the screening quality, such as the percentage of positive cases, the median MoM of the different markers and screening test effectiveness.

This new version fully adapted to operate in local networks, intranet and internet in an environment of multiple centres and users, uses SsdwLab’s classical and widely proven, robust calculation engine and incorporates significant improvements regarding connectivity to auto-analyzers, laboratory information systems (LIS) and corporate database. As in previous versions, an open database (unprotected) has been used, but security and robustness has been widely improved thanks to the replacement of MS Access 2000 with MS SQL Server 2005 which, in practice, has no limits in its growth.

It also has an interface web access compatible with any current browser and operating system with Adobe Flash installed, it can be translated into any language due to UNICODE support, it allows an almost unlimited number of users working concurrently on a single installation and makes it possible to assign specific ultrasound marker medians to each sonographer as well as the use of the new case-by-case quality controls such as CUSUM.

This revision (1.0) of version 6 incorporates prenatal detection, during the first trimester of gestation, of early and late preeclampsia, as well as the screening for trisomies 21, 18 and 13 independently, and a substantial number of improvements both in the User and in the Configuration screens.

The total user-configurability of this Software, as is usual in our computer applications, allows us to apply most innovations in the area of prenatal aneuploidy screening, by means of our programs and their updates, to biochemical or biochemical-ultrasound screening tests.

SsdwLab User Guide includes, in most chapters, a section called How to make / perform a New… where all practical aspects for executing the software applications are displayed. These sections constitute a real basic user’s guide, and should be first consulted for the solution of any doubt or for the sake of learning better how to perform for the first time any of the multiple options that SsdwLab offers.

The hope that this new revision, which incorporates the latest innovations published in the broad area of prenatal detection of congenital anomalies, will contribute to the improvement of the clinical performance of prenatal aneuploidy screening.

Girona, February 2014
SsdwLab6. Specifications

Characteristics of SsdwLab6


- Usable in Microsoft XP (with SP2), Vista, Windows 8 and later versions, on a single workstation or a network.

- The reliability and accuracy of the algorithms and internal mathematical calculations of SsdwLab6 have been checked using the prenatal screening software: Prenatal Screening Decision Support QA Tools version 2.0 from Media Innovation Ltd, partnership of University of Leeds and UK National Screening Committee (http://www.media-innovations.ltd.uk/dsqainfo) which constitutes a leading program for the validation of trisomy 21 screening software programs in the United Kingdom.

- Database Microsoft SQL Server 2005 for Windows, which guarantees compatibility with other systems and the analysis and treatment of the data (unprotected) by means of other commercial software for database administration. See the section on limitations in this chapter.

- Automatic adaptation of dates in the different international formats according to Windows Regional Settings

- On-screen display in multiple languages.

- Hardware protection against copying, unauthorized access, etc. (by using a USB Hasp HL key) and software protection (multiple security levels by means of user code and password with expiration date) of access to records, changes, configuration, printing, etc.

- Historical and log file containing new patient records, modifications to patient records, identification of the user who has carried them out as well as the date and time. To comply with legislation on security measures for automated files which contain data of a personal nature (Royal Decrees 994/1999 of June 11 and 195/2000 of February 11) and patient rights (such as Law 21/2000 of December 29 from the Generalitat de Catalunya on rights
concerning health, patient autonomy and clinical documentation). Control and automatic recording of Program inputs and outputs by different users, both on single workstations and networks.

- Record of accreditation of the sonographers who assess ultrasound Gaussian markers (those which are biometry-related) and configurable lock on those whose accreditation is not recorded.

- Definition of an unlimited number of Screening Profiles with simultaneous use of up to 10 biochemical and/or ultrasound markers with known Gaussian distribution and correlation coefficients, as well as up to 15 dichotomous markers with known positive and negative likelihood ratio for trisomy 21, and another 15 dichotomous markers for trisomy 18, and the same number of markers for trisomies 18, 13, early preeclampsia and late preeclampsia.

- Lock on the configuration of all the parameters in the Screening Profiles and prevention from being deleted when they have been used in the calculations of a screening record. A new Screening Profile can be defined, using any of the existent ones as a base, although their configuration is locked.

- Biochemical and ultrasound markers, correction factors, units of measurement, cut-off levels, truncation limits, population parameters, etc. can be fully configured and defined by the user.

- Calculation of gestational age using any of the following parameters: date of last menstrual period, ultrasound or biometry (CRL, BPD, FML, etc.) estimation of weeks and days of gestation at a certain date, and conception date.

- Definable and customizable configuration for each computer in a network environment.

- Ability to select the method of *a priori* maternal age risk estimation.

- Selection of the point at which risk is estimated (at term or at the time of the test); and in the latter case, possibility of correction for intrauterine lethality by means of discrete method (in a specific week) or continuous (variable according to gestational age, expressed in days, from a polynomial formula revisable by the user).

- Estimation of "age-marker" combined risks for trisomies 21 (T21), 18 (T18), 13 (T13), preeclampsia (PE), early preeclampsia (EPE) and late preeclampsia (LPE) for each individual marker and for the combination of all of those used in each Screening Profile in the first and second trimesters of gestation. Very complete information, in the same screen as the Risk calculation result, about the median values of each marker, likelihood ratio (LR) and partial Risk Index for each marker, for the trisomies and for preeclampsia, as well as the combined LR for all the markers used, the point at which the risk is estimated (at the time of the test or at term), combined risk only for Gaussian markers (when dichotomous
markers are used simultaneously), maternal age at the expected
delivery date, total days (and weeks and days) of gestation for
each marker used (very useful in sequential screening),
gestational age corresponding to a biometry used with an
ultrasound marker, method of evaluation for the markers with
positive and negative LR, etc. This information is presented in
floating tool tip text to avoid an excess of active visual information.

- Estimation of neural tube defects (NTD) risk by means of a MoM
cut-off using the second-trimester maternal serum alpha-
fetoprotein.

- Ability to use only some of the markers included in a Screening
Profile and to store some or all the values for investigation, median
calculation, modelling, etc., without their intervention in the risk
calculations or appearing in the printed Report. This is very useful
in first-trimester twin screening if we want to calculate Risk only by
means of NT, but want to have the values of the biochemistry for
later.

- Option of using constant or variable population parameters
according to gestational age (mean log 10 MoM for the trisomies
and preeclampsia).

- Optional calculation of the aneuploidy risk in twin pregnancies with
the centre’s own population parameters, and differentiation of
chorionicity (the so-called SsdwLab5 method).

- Automatic median calculation from data obtained in the screening
laboratory, as well as calculation of the polynomial function (up to
quartic, weighed for the number of determinations in every week of
gestation or interval of a biometry) between the gestational age (in
days), or a biometry in millimeters, and the value of each marker.
Possibility of applying a reciprocal, exponential, $10^x$, log e or log
10 transformation to the polynomial function or the variable x.
Possibility of direct input of the medians to carry out the same
calculations in the biochemical markers.

- Ability to manually input the multiples of the median (MoM) in the
Risk calculations for verification of the calculation corrections and
quality control (UK NEQAS, etc.).

- Correction using a previous pregnancy affected by a trisomy, NTD
or pathology which has an influence on the development of
preeclampsia.

- Selection of the correction method for the patient's weight
(exponential ($10^x$) or reciprocal) and automatic calculation of the
correction factors (coefficients) and the median of the patients’
weight (from the database) in both methods.

- Automatic calculation of the Median of the multiples of the median
(MoM) for each Marker, corrected and uncorrected by the
correction factors and maternal weight, as a parameter of
screening quality test.
- Automatic calculation (from the database) of the correction factors (covariables) for the 15 user-definable.
- Automatic calculation (from own program's database) of the population parameters of Gaussian distribution of each marker (median and standard deviation), when there is a sufficient number of tests using the marker.
- Automatic calculation (from the database) of the correlation coefficients among pairs of markers, when a sufficient number of screenings have been performed using the marker.
- Automatic calculation of the Percentage of Positive Cases, median of the MoM of each marker and of the effectiveness of the screening test (sensitivity, specificity, etc.); in the latter case, if the perinatal result is reported.
- Ability to access a Server which contains the patients' filiation data; automatic input of these into the database and Program screens.
- Fully customizable report, with the possibility of including a logo in the header, printable in any language which uses the western alphabet.
- Possibility of printing graphic charts in the report that guide visually about the Risk level for maternal age and trisomies.
- Automatic system for exporting selected screening records in the standard system.
- Visual calendar for the input of dates, no need to type the digits, in order to avoid the frequent errors in this type of field.
- Thorough control of errors. Automatic correction of certain typing errors in data input or on-screen display of informative dialog boxes (message requiring a certain action) about the type of error when the Program suspects, or finds out, that there is some type of error in the data entry or calculation processes, recording of records, printing, information importing-exporting, violation of access privileges, etc. If the error persists or compromises the result of the risk estimates, these will not be displayed or printed.
- Optional registration of requesting doctors and hospitals, indications and results of invasive techniques, ultrasound findings, Perinatal results for quality control, etc. All totally configurable and user definable.
- Quick search for patients or episodes by Surname, Name, Health Record number, NIC or PIC, indistinctly.
- Automatic estimation of the typical parameters for screening effectiveness (sensitivity, specificity, etc.) from the database of patients who have already been tested, as well as possibility of hypothesis formulation with different risk cut-off levels.
- Very complete help.
Limitations of SsdwLab6

- **At User Level**
  - Using this Program requires User Training and specific Knowledge. Without such knowledge and training, the program should not be used!

- **Imposed by Microsoft SQL Server 2005 database.**
  - Maximum size of 4 Gbytes for the Program database files if the Express version (free) is used.
  - Unlimited maximum size for the Program database files when using the Professional, Standard or Enterprise version (commercial)

- **Up to 255 simultaneous Users**

Neither the user-level limitations nor those imposed by Microsoft SQL Server 2005 are insurmountable obstacles. In the first case, SBP-SOFT 2007 S.L., among others, can provide information and theoretical and practical training on how to use the Program, prenatal diagnosis of congenital anomalies, and aneuploidy and preeclampsia screening.

Regarding the conditions imposed by Microsoft SQL Server 2005 specifications, it has been verified that the SsdwLab6 program can manage up to 1,000,000 patient records, (database SSD52IS.mdf) and that it is possible to consult, modify and add new screening records without operation anomalies. It can also Compact and Repair a database of this type. As a security measure it is advisable to make a backup of the logs file of the database of the Program (SSD52IS_log.ldf) every 6 months, which should be saved and deleted from the working directory, so that the Program can create a new empty database.
General Information

This version of the Program is presented on CD ROM and includes different directories for the different languages that the Program supports (SPANISH, ENGLISH, etc.). Automatically, the CD ROM installation program detects Windows configuration language in the computer and it displays the Setup screen in the language used by Windows.

In addition to the directories where the installation files for each language are located, there is a directory called “HaspProDriver” where the USB key’s installation file type HASP HL and the directories “MS_NetFramework_2_0” and “SQL_Server_2005_Express_AS” are located. In these directories the files for the installation of MS .NET Framework 2.0 and SQL Server 2005 are respectively located in their Express version. Moreover, in the directory AdobeReader_9 we can find the Adobe Reader installation file, which is necessary for reading and printing the reports in PDF format.

Minimum Requirements

We will distinguish between minimum knowledge requirements for the person responsible for the use of the SsdwLab6 program (from now on, ‘the Administrator’) and those on the level of Hardware and Software.

Administrator

Using this Program requires User Training and specific Knowledge in prenatal diagnosis and aneuploidy screening. The Program must not be used by anyone who lacks the sufficient knowledge!

Remember that SBP SOFT 2007 S.L. can provide Information and theoretical and practical Training on the methodology for prenatal screening for aneuploidies and preeclampsia and on the adequate use of SsdwLab6.

Hardware

A PC-compatible computer with a Pentium processor, or equivalent to 1 GHz, with a minimum of 1 Gbyte of RAM memory.
It must have a CD ROM reader, 300 Mb of free space in the hard disk, 1 USB port available and a screen resolution of 1280 x 960 pixels.

We strongly recommend that a UPSS (Uninterrupted Power Supply System) is available in order to avoid corruption of the databases in the event of power supply failure.

**Software**

Operating System: Microsoft Windows XP 32-bit (SP2 or later version), Vista, Windows 8 or later version. Regional configuration for a western country with international alphabet. It is highly advisable to configure the date with four digits for the year. It is essential to have Microsoft SQL Server 2005 Express installed and it is advisable to have SQL Server Management Studio Express (both free, existing in the Installation CD ROM) as well as Microsoft NET Framework 2.0 (usually included in Microsoft operating systems from XP Service Pack 2). In order to view the printed reports, ADOBE Reader 9 or later version must be installed (either free download from the ADOBE WEB, or install from the CD ROM’s directory), providing it is not already in the user’s computer.

Having a continuously-updated Antivirus program and the periodic creation of backup copies is very important in order to avoid possible loss of secondary data because of the unnoticed access of intruders.

**Installation of the program on the computer**

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Connection and characteristics of the HASP HL key

The HASP HL key, provided with the Program CD ROM, must be connected to an available USB connection on the computer and it is necessary to run SsdwLab6. In the case of an installation of a dedicated server the HASP HL Pro key must be only connected to the server.

The SsdwLab6 program’s HASP HL key is of the "Pro" type, with an internal memory of 112 bytes and a unique identification number specific for each key. When it is connected to an active USB port, a red LED on the key is illuminated, indicating that a good connection exists with the computer. To confirm that the operating system recognizes it, we access the "System" option on the Windows "Control panel". By clicking the "Device Manager... " command in the "Hardware" folder and opening the "Universal series bus controllers", its presence should be viewed as "Aladdin USB Key", which is the name for the HASP HL keys distributed with the SsdwLab6 program.

Unlike other USB devices, it is not necessary to perform the "Disconnect or eject hardware" action in order to remove the key from the computer, since the machine recognizes this without issuing any message.

Running the CD ROM contents

When we insert the CD ROM into the drive of the computer, the CD ROM installation program will automatically detect Windows’ configuration language in the computer and display the Set up screen in the language used by Windows.

Two options are provided:

The first option allows us to “Install the HASP HL key software” which we must choose first and follow all the wizard’s steps until the key’s drivers have been installed. Once this software has been successfully installed, the HASP key, provided with the program, must be connected to an available USB port and if it works properly (the software recognizes the key) a small red light at the end of the key is illuminated. Some installations use a virtual Hasp key built into the software that doesn’t require physical installation.

The second option allows us to “Install the SsdwLab Program version 6” either on a single computer, or on a server, or on one or several client computers which will share the same database in a server (which must also have the SsdwLab6 Program installed). When starting this option, a wizard is shown requiring first the acceptance of the licence agreement, then it suggests the directory, by default, where all the program files will be installed and can be modified by the user. During this installation phase, which begins when you press install, it is detected automatically whether the computer has Adobe Flash Player installed, and if it doesn’t, it gets installed and once finished, we must press Close.
on the Flash Player window, so that the installation of the SsdwLab6 program can continue.

During the installation process of the SsdwLab6, a window is displayed where we must choose if we want the installation as a Server (the same as for a single computer) or as a Server dependent client.

On the “Connect to SQL Server” screen we must enter the credentials to access the SQL Server 2005 engine.

Server name: IP or name of the computer that has the SQL Server engine that the program will use. Its default name is “localhost”, which identifies the computer into which the installation is being carried out, and where the installations will go as a Server and as a single computer. In the case of installations as a server dependent client, you must indicate the IP or name of the computer where the SQL Server’s engine has been installed (the Server’s computer), which for example can be of the type:192.168.1.3\SQLEXPRESS or PC_Server\SQLExpress, always with SQL Server’s specific syntax. The installation program will always try to detect SQL Server’s available installations and will show their names in a combo box in “Server’s Name”. If in doubt, the database Administrator should be consulted.

Authentication: Security type that the SQL Server engine has installed.

Windows authentication: Does not need user name or password. It’s the one that comes preconfigured with Windows 7 and Windows Vista. (Ideal for monoPC setting).

SQL Server authentication: needs a user name and password to access the SQL engine. (Required for network installations)

After selecting the server Name and the authentication parameters, you must press OK. The program will verify that you can really connect to the database and in this case it will go on with the installation.

When the type of installation is as a server, at this point the installer generates the database, initializes it, and once finished, it displays an alert indicating that the configuration has been completed successfully.

With Windows Vista and later versions, you must run the SsdwLab6 installation file or setup_ESP.exe (or the corresponding ones in the different languages found in the directory with your language name) “as Administrator” (default option of the Setup Wizard or by right-clicking on the file. Otherwise, errors may occur during installation just before the installation of the Adobe Flash Player.

Uninstall

Uninstalling SsdwLab6 Programs is really simple, by using the “Add or Remove Programs” option, located in “Control Panel” in
Windows XP, Vista, 7, 8. The screen provides all the information needed to carry out this process successfully. When the Program was installed in a directory different from SsdwLab6, manual removal of the chosen directory may be necessary.

The HASP key drivers are removed by using the same setup program: HASPUserSetup.exe from the CD ROM directory.
Running the Program

SsdwLab6 Program Access. Start Screens

Running the Ssdwlab6 menu in the Windows Start Menu (SBP Soft 2007; Ssdwlab6; SsdwLab 6 Prenatal Screening Management) or clicking the “SSD6” icon that is shown on the Windows desktop starts the Program when it has been installed as a single station or as a server.

When it is installed as a client, with a database in another computer (normally a server), during the installation process the Program will ask for the location of the instance of SQL Server that we wish to connect to, and which must normally be entered in the following formats: 192.168.1.3\SQLEXPRESS or PC_Server\SQLEXPRESS, etc. In such cases, it is very important to contact SQL Server 2005 Database Administrator, who will inform us on the specific syntax of the connection.

The first screen asks for the user code and password of the person who is going to access the program. The password is case sensitive and therefore the characters must be entered.
adequately. It is highly advisable to change the password, which should be done the first time we use the Program, otherwise unwanted access to the Program might occur and the history and log files would not reflect a faithful usage by each user.

By clicking the Enter button, the user’s data are checked by the server and if these are correct the following screen corresponding to the beginning of the program as such will be displayed. At the top of the screen, the selection of the different menus appear, and in the central part there will be access buttons for the most frequently used options such as Screening and Post-Screening search, Patients Search, Add New Patient, choosing the type of start screen and changing password. When the function of these buttons is repeated on the drop-down menus at the top of the screen, their description will be in the order that corresponds to those menus and submenus.

Access to the various menus and options will depend on each user’s privileges or restrictions and they can only be modified by the application’s Administrator. The different menus on this screen will remain visible in the remaining screens of the program, and will normally be accessible from any of them.

**Change Password**

Each user’s password is secret and no one knows it, not even the Program’s Administrators, so if a user forgets their Password nobody can remind it to him/her, and in this case the only option is to “Reset” the password (to delete it) and he/she will be assigned a new provisional password which should be modified the next time that the Program is used.

This is the option, located on the lower left angle of the main screen that allows us to modify the Password and enter a new one when the Program warns the user that it will expire. This happens immediately after you’ve accessed the program for the first time, and after a certain amount of time in order to avoid unwanted visits.
The procedure is really simple. The user must enter the current password, the new one and repeat the new one, which must have at least 6 characters (letters or numbers or a combination of both). Remember that passwords are case-sensitive.

*Resetting* a password can only be done by a System Administrator providing that they have the necessary permissions.

![Change Password](image)

**Common elements in the Start screens**

These screens allow the management of administrative data of the different patients recorded in the system (entries, modifications, deletion, arrangement and search). It also allows a specific patient (and all her screenings) to be considered as a test or quality control (Mark as test). Depending on the configuration of the program, certain fields may be accessible or not, in which case the information is normally not relevant for the screening calculations.

Most of the start screens are divided into 4 main parts, which we will describe separately: the upper toolbar for menus and icons, the icon toolbar located on the right side of the screen, the data grid, and the left column for searches and filters.

In most cases, the different parts of the screen, which we will normally call windows, have a separation between them that allows, by dragging a small element in the middle of the separation, to rearrange their size.

**Upper toolbar for menus and icons**

The drop-down menus allow access to all the Program’s functions. The icons allow the change of language of the screen texts, full screen viewing, access to Start screen and exiting the Program. Further on we will deal with the function and description of the menus which are unfolded from the top of the screen.

**Icon toolbar on the right side of the screen**

This area of the screen has a series of icons that allow quick and direct access to the following screens and functions: general
Patients Search, general screening and post-screening search, add a new patient, update a patient’s data when these may have been modified by another user, and close the current screen.

Data grid

In this grid all existing patients in the database are shown in tabular form, as well as the ones that have been selected by using the Patients Search filter on the left column. At the top of the grid, on the right side, is presented the number of pages of existing patients, and on the left there is a mechanism for navigating through the different pages.

In the outermost top right of the grid there is a small yellow star. Clicking it, displays at the bottom of the grid information concerning the speed at which results are sent and returned as well as the number of lines (records) per page and the possibility for this number to adjust automatically.

The different columns of the grid are headed by the name of the field that they correspond to (in general, the field names are made up with their English equivalents preceded by a suffix that gives information on the field type).

Left column for search and filters

This section deals with the arrangement, search and selection of patients based on their demographic characteristics or on their order of entry into the database.

When the box for “Automatic Update” is checked, or when clicking the “Search” command, all the patients in the database, and not only the ones that can be viewed in the first page of the grid, will be arranged according to the criteria in the two drop-down lists immediately below the search command, this is to say, we can define the criterion used to arrange the patients in the first drop-down list, and the direction of this arrangement – ascending/descending- in the second list.
On the other hand, we can choose to display only the patients who meet certain criteria defined from the filters, or searching conditions which are applied through the corresponding controls.

Screening Administration. Add a New Patient

This is the program’s most complex screen because it displays, in a double window, each one with different folders, all the information concerning a patient’s screenings for her different pregnancies, as well as the data, if existing, concerning any invasive techniques practised, ultrasounds for malformation detection and each one of the fetuses’ perinatal result (up to a maximum of two) from each pregnancy.

All the information is presented, as mentioned above, in two windows, a narrower one on the left that works as an informative summary of the patient’s administrative data (Patients Folder and Post-screening folder) and of all the ones from the right window (Menu folder), and a larger one, to the right, with multiple folders in whose controls is stored all the information concerning the pregnancy, screening type, biochemistry, ultrasonography, gestational age, screening result, which will be described below. This is the “Screening Window”. Both windows present a separation between them which allows, by dragging a small element situated in the middle of this separation, to modify their size.

On the top right side of this screen we have, as in the previous screen, a group of icons that allows quick and direct access to the following screens and functions: general search for screenings, consulting a specific screening of the patient selected in the grid, updating the patient’s data when these may have been modified by another user, and closing the current screen.

Summary window

This window occupies the whole left side of the screen and has two folders: Screening and Post-screening. The selection of each one displays respectively, in the Screening window on the right, the folders for Screening in the first case (Patient, Pregnancy, Screening, Biochemistry, Ultrasound, and Risk) and the folders for post-screening in the second case (Patient, Pregnancy, Invasive Technique, Morphology Ultrasound and Perinatal Result).

The Summary window displays, moreover, a very complete summary of the most important aspects of the patient’s Screening (and Post-screening if we check the tab for this folder), such as demographic data, pregnancy record, screening record, type of Profile used, GA, calculated Risks, markers used, correction factors, dichotomous and invasive techniques markers, morphologic ultrasound and perinatal result (if the Post-Screening tab is checked).
Screening Window

In this window we first find the following folders: Patient, Pregnancy, Screening, Biochemistry, Ultrasound and Risk.

Patients Folder

In this part of the screen appear the data concerning the selected (highlighted in blue in the grid) or newly added patient.

The buttons located at the top of this area allow the functions Add, Edit, Delete, Save and Cancel the data input of the patient that has been selected or added.

Each control in this area has its own characteristics so that the ones concerning name and surname always use capital letters, the one for birth date allows the use of a calendar (as practically all the ones for dates), the ones for race, ethnic group, country, etc. offer a choice from a drop-down list, etc.

For the system to accept a new patient’s entry, it is required at least to fill in the obligatory controls for name, surname and birth date, and one of the four identifying fields corresponding to Social Security Number, NIC, PIC and CIC. If there is an attempt to duplicate an already existing record with the same NIC, CIC or SSN, the system will inform us about that fact.

Checking the box “Mark as test” makes all the information concerning a specific patient and her screenings to be considered by all the program actions as a test, or a quality control, so that none of her data will be taken into consideration for statistic calculations.

While Race only admits 4 options, all the other text boxes with a drop-down list (ethnic group, country of residence, birth country and insurance) can be defined and configured by the system’s Administrator. In all of them, the fact of choosing the first element in the list (empty) means “Not Evaluated”. One novelty is that all the combo boxes in the program allow inserting a search text consisting of one or more characters. These will be preselected, in any position, for the search among all the terms in the list. This will
greatly facilitate the search for the terms that interest us, even in the list with a numerical code at the beginning of each text in the list.

When a new patient’s record is created, and after entering her data, we save it by clicking the “Save patient” button and her data are displayed on the top left side of the grid as a newly entered record.

**Pregnancy folder**

This folder allows unequivocal identification of the pregnancy of the patient undergoing a prenatal screening for aneuploidies or preeclampsia, and it allows us to enter the relevant and accessory information characteristic of that pregnancy.

At the top it indicates the order number of the pregnancy on display (in the case that the patient has been screened for more than one pregnancy, you can select among them), and displays the Add, Edit, Delete, Save and Cancel buttons which perform the actions that their names suggest and must be necessarily used if we want to enter or modify a patient's pregnancy, as happens, as we will see further down, with all the remaining folders because the database is in a server away from the client where the data are entered and they have to be sent to the server to verify their correctness before storing and processing them. Clicking Add allows data entry.

The only data of indispensable completion are: number of fetuses (1 by default), but it is advisable, and in certain configurations essential, to indicate the patient’s weight (at the time of drawing the blood sample for biochemistry), and the number of cigarettes per day in a smoker patient or “0” to verify that she does not have this habit.

Moreover, due to the increasing egg donation or embryos in assisted reproduction, this possibility has been contemplated, so that the maternal age risk can be calculated based on the donor instead of on the recipient who is the subject of screening.

This folder contains several frames, with their corresponding names: Pregnancy identifier, Egg source and Pregnancy type, Single-double Gestation, Weight / Height / Body Mass Index (BMI), Last Menstrual Period / Conception date, Smoker / Folic acid and Male Parent’s data.
Pregnancy Identifier

The first control is used to identify the pregnancy by the number of obstetric process in the centres that are using this nomenclature.

The control for the obstetric formula allows its input (term deliveries / premature childbirths / abortions / live children) in such a way that the separators are entered automatically (depending on the Program configuration) after the input of two digits (two digits have been assigned for the nowadays rare possibility for a woman to have more than nine pregnancies) for each of the numbers of the formula as in the following example: “02/00/01/02”.

Egg source and pregnancy type

When the egg or eggs of the current pregnancy come from the screened patient herself, the Maternal Age Risk (always at term) is calculated from her birth date, while when the egg or eggs come from a donor, the Maternal Age Risk (also at term) is calculated from the donor’s age, which is the age at donation adding approximately 9 months (38 weeks or 8 and a half months to be more precise). This is the reason why when we select “donor’s” eggs, a box with new controls appears where it is necessary to enter the donor’s age at the expected term date (with the decimal fraction of the months), or her birth date (both options are selected from a drop-down list) and the Maternal Age Risk will be calculated from this age or birth date. This information will also appear in the printed report.

The pregnancy type is an informative field, not always obligatory, which can be selected from a drop-down list customizable and modifiable by the system’s administrator.

Single-Double Gestation

This information is very important for the program because, as will be seen throughout this user’s guide, Risk calculations are very different depending on whether it is a single or a double gestation. The other multiple gestations (triple, etc.) have not been taken into consideration, because the current biochemical prenatal screening is not applicable to them.

The program has, by default, the combo box of the Number of Fetuses corresponding to a single gestation, because it is the most common one, and it just has to be changed to “2” in the case of a double gestation.

In twin pregnancies, knowing the chorionicity (type of placenta) allows a more precise Risk estimation as well as the use of specific population parameters in multiple gestation fetuses. In monochorionic pregnancies the calculation of a single Risk is accepted (pseudo-risk) for both fetuses, while in dichorionic, especially when fetal ultrasound markers are used, the specific risk for each fetus should be considered.

Thus, knowing the placentation type, in a double gestation, is very important, as monochorionic twins are always monozygotic, which means that the chromosomal affectation of one implies, almost for sure, the same affectation of the other twin, and in this case, even
if there are Gaussian ultrasound markers in the Screening Profile, such as nuchal translucency, only one Risk calculation is performed for both twins (pseudo-risk) and it is advisable to input in the Program the fetal length (CRL) of the largest fetus and the median nuchal translucency (NT) of both fetuses (both parameters are automatically predetermined from the configuration defined in each Screening Profile). On the other hand, dichorionic twins tend to be bizygotic, although a small percentage are monozygotic. Both in monochorionic and in dichorionic twins, when the Screening Profile has Gaussian markers, such as a nuchal translucency, the program will show two controls for the ultrasound (one for each fetus), in which the respective biometries (CRL) and the NTs must be entered. In monochorionic gestations a unique Risk (pseudo-risk equal for each fetus) will be printed, whereas in dichorionic gestations one specific, normally different, Risk for each fetus will be printed.

When in a twin pregnancy the type of placentation is unknown, the Program considers it dichorionic for all purposes because it is the most common one, and performs the calculation as if it were this type.

**Mother’s Measurements (Weight / Height / Body Mass Index)**

The patient’s weight is of great importance in Risk calculations, especially for biochemical markers for which it is a correction factor. This is because these markers are produced by the fetus or the placenta and they dilute in the maternal serum and its volume is proportional to the weight of the patient. It must be expressed in kilograms and has its own range control in order to avoid error if extremely unlikely values are entered. Depending on the Program’s configuration, in this section it may be necessary to input the weight, so that the Risk can be estimated.

Nowadays the patient’s height is not taken into account for the Risk calculation for Aneuploidy but it is used in the risk calculation for Preeclampsia. It must be expressed in centimeters.

The Body Mass Index (BMI) is calculated automatically, if the patient’s weight and height have been entered.

**Smoker / Folic Acid**

Smoking during pregnancy has been proven to modify serum concentration of some biochemical markers. This is why this correction factor should be appropriately assessed to increase the reliability of Risk estimates. To enter this datum, a drop-down list is used, with a list where you can select from “0” (non-smoker) to “> 40” (unselected meaning Not Assessed).

The program assumes that a patient is a smoker if 5 or more cigarettes/day have been registered. This limit can be modified by the system Administrator in the Screening Profiles, as it has not yet been proved, among other important aspects, which is the minimum amount of cigarettes that affects the concentration of each marker.
The information on the ingestion of folic-acid before conception may have an epidemiologic or scientific interest, but it is not used for the Risk calculations.

**Male Progenitor’s Data**

The set of data concerning the fetus’s male progenitor (age, birth country, race and ethnos) do not have an influence on the Risk estimates nowadays. However, they are an interesting research matter, so they are included here, facilitating the prospective selection to those who may be interested in the research.

The text boxes with drop-down lists are used just like the fields with the same name for the mother, while the age should be entered here in complete years as they are not automatically calculated from the birth date.

**Screening Folder**

This folder allows the selection of the type of screening to be carried out (Screening Profile) and depending on the selection of the type of screening (aneuploidy or preeclampsia) its selection displays a variable series of parameters such as its date, screening centre, requesting doctor and signatory, type of consent formalized by the patient, the present or absent correction factors (covariables), manual input of Gestational Age, Previous Congenital Anomalies, Dichotomous Markers (Maternal antecedents) and Blood Pressure in the preeclampsia.

At the top we find the order number of the screening displayed (when more than one screening has been practised on the patient, you can select among them in the gestation displayed ), and it has the “Add”, “Edit”, “Delete”, “Save” and “Cancel” buttons that perform the functions that their names suggest and are present in all the folders. “Add” allows data inputting.
Screening Data

It contains, by default, the current date, and allows us to enter the date when the screening is performed, which must always be the Date when the blood sample was taken from the patient for the biochemistry (**very important**). The Screening Date refers to the specific day when the screening is performed (as in the screenings in one single step, usually the biochemical ones) while for those performed in two steps (as is often the case in biochemical-ultrasound screenings) the date must refer to the blood sample draw for the biochemistry. It is also possible to add an identification corresponding to the record number of the Screening Centre.

Centre / Profile

Selecting the Screening Profile Type affects the type and amount of information displayed in this folder, as well as the number of frames with controls, depending on whether we select a Profile for the screening for aneuploidies (T21, T18, T13) or for the screening for Preeclampsia (EPE or LPE). This selection is the first operation that we must do in this folder; otherwise some groups of information (frames) might appear or disappear once we have entered the information.

The type, number and order in which the Profiles appear in this drop-down list, depends on the Configuration defined in the “Screening Profiles” menu (“Administration” menu and “Calculation Variables” submenu), as will be explained in detail in the section corresponding to the configuration of the Screening Profiles. This drop-down list will only display the “Active” profiles, that is, the ones that we will be able to use in the risk calculations.

The Centre appears by default but in case the user has the appropriate permission he/she can choose among the different Centres he/she has access to.

Correction Factors observed

This section contains all the Correction Factors (covariabes) defined for to the type of screening of the Profile selected in this folder. Those which have already been entered in the previous folders (like Race, Tobacco, etc.) will appear as assessed (Yes, No, Not Assessed), while those which have not been entered, because they don’t exist in the previous folders, such as Insulin-dependent Diabetes, can or have to be entered in this section. The need to complete each and every correction factor depends, the same as for the patient’s weight, etc., on the general configuration of the Program which can only be modified by the Administrator.

Previous congenital anomalies

In this box we can enter, by means of drop-down lists, the trisomy and NTD antecedents, depending on the configuration of the Screening profile, which the patient has had in previous pregnancies. These antecedents have a great importance in aneuploidy Risk estimation, which increases with positive
antecedents, while nowadays they do not have an influence on the risk for preeclampsia.

**Requesting doctor / Signatory**

These two drop-down lists allow you to select the name of the professional who “requests the screening” and the name of the one who “will sign the printed report”. By default, they may have predetermined names and may also have the name of the Requesting Centre, or it can be entered.

**Screening Consent**

This section contains 3 dropdown lists and a check box (depending on the general configuration) which allow the Program to show respectively whether the patient accepts the requested screening, whether she has been adequately informed about the screening method and finally whether she has signed a written document of Informed Consent. If we select this check box, it allows us to inform that the screening has been Suspended (ended before being complete) and in this case we can select one of the multiple reasons for the suspension from a drop-down list located on the right.

**Dichotomous Markers for Maternal Antecedents**

Here we find, only in the Preeclampsia Profiles, a set of dropdown lists that allow us to inform the Program about the maternal antecedents that affect the development of preeclampsia. For each one of them we can select Yes, No or Not Assessed (empty). If we click the underlined text in blue “Mark all = Not”, all the drop-down lists will have the “No” value, which facilitates a manual input of data in the most common cases with no antecedents of any type.

**Gestational Age**

We must use this check box when we need, or decide, to manually input the Gestational Age by entering the weeks and days informed by an “Ultrasound” performed on a specific date. When we check the box it displays the boxes for Weeks and Days and the date when it was assessed using the mentioned ultrasound. It is also possible to just enter the total number of gestation days (not the weeks), if known.

**Blood pressure**

The maternal Blood Pressure values are essential in the screening for the Preeclampsia. This is why this box only appears in the profiles of this type of screening. The date of the measurement is also essential.

It is highly advisable to take both systolic and diastolic blood pressure twice during the pregnancy using an automatic blood pressure monitor, the patient sitting down and both arms resting at the same level as her heart and after she has had a reasonable period of relax. We enter the values in the corresponding text boxes and to the right of each determination the Mean Arterial Pressure (MAP) which consists in the following formula:
(systolic AP + (diastolic AP *2)) / 3

The median of all the determined MAP is displayed automatically to the right of the Date of the measurement (MAP tag) and, once we have saved the contents of this folder, the Multiples of the Median (MoM) calculated for this biophysical marker are displayed in the top right end of the box.

**Comments**

Free text can be used here to describe any comments that may arise as a consequence of the performance of the Screening and which cannot be included in any other section of this folder.

**Biochemistry folder**

This folder is used to input the data of the Biochemical Markers and has four frames: "Blood Test Data", "Laboratory", "Gaussian and Biochemical Markers" and "Comments". At the very top are the Edit, Save, Cancel and Validate buttons (depending on the general configuration), with the functions that their names suggest. We press “Edit” for data input. Once we’ve saved the data, we click “Validate”, to confirm that the data have been verified by the person authorized for that purpose and prevents further modifications (unless we click “Undo Validate”).

In twin pregnancies of any type a sole set of Blood test values appears, as the maternal blood sample is shared by both fetuses and each one’s participation in the concentration of the different biochemical markers is unknown.

**Blood test Data**

It allows you to enter the Sample Date as well as its identification by the Laboratory. The date will generally coincide with that of the screening but it may be different and there may even be a different date for each marker and in this case we must tick the “Specify Dates” check box located at the top of the Gaussian Biochemical Markers box, which displays a specific date before each marker that must be completed (as in the case of Integrated test).

**Laboratory / Sampling Module**

It allows you to select the identifying names of both units using two combo boxes that can display, depending on the configuration, pre-selected names.
Gaussian Biochemical Markers

Here we enter the quantitative values of the Biochemical Markers of the Profile that is being used for the screening in the corresponding units. By clicking “Save”, the MoMs will be calculated and displayed. In addition, by placing the cursor on the MoM of the marker, a very complete informative box will be displayed about the calculation process with this marker, the values of the MoM without corrections, the likelihood Ratio, etc.

Comments

Free text can be used here to make any comments that may arise concerning the biochemical screening and blood sample draw which cannot be included in any other section of this folder.

Ultrasound folder

This folder, intended for the input of the Ultrasonography data, has six frames: “Ultrasound Data”, “Ultrasound unit / Sonographer”, “Biometry”, “Gaussian Ultrasound Markers”, “Fetal Dichotomous markers” and “Comments”. It has the following buttons: Edit, Save, Cancel and Validate (depending on the general configuration) for the actions that their names suggest. The “Edit” button allows data input. By clicking “Validate”, once we’ve saved the data, we confirm that the data have been verified by the person authorized for that purpose, and prevents further modifications (unless we click “Undo Validate”).

In twin gestations, a single Ultrasound folder is shown, but it has a double number (one for each fetus) of controls for the fetal ultrasound parameters.

Ultrasound Data

It allows the input of its date as well as this test’s identifier. Generally, the date will not coincide with the screening’s date.
Ultrasound Unit/ Sonographer

It allows you to select the identifying names of both (unit and professional) by using two combo boxes which may have, depending on the configuration, pre-selected names. Selecting the sonographer’s name will be obligatory when, according to the configuration of the program, his/her accreditation is required for the evaluation of one or more ultrasound markers, such as Nuchal Translucency (NT).

Biometry

This box allows the input of the fetal biometry obtained from the ultrasound and displays the different biometries which were predefined in the configuration of the Profile used and that were used for the calculation of the Gestational Age (GA). The check box located before the biometry allows you to select which one will be used for the automatic calculation of the GA (it can be defined in the Profile configuration).

When we save this folder, the GA calculated by the biometry on the date when the ultrasound was performed is shown on the right of its respective biometry.

In twins, this folder calculates automatically the gestational age of both fetuses (both in monochorionic and dichorionic twins) using the biometry that has been defined in the configuration of the Profile used (higher, lower, arithmetic mean, etc.)

Ultrasound Gaussian Markers

This folder is for the input of the quantitative values of the Profile’s Ultrasound Markers that are being used for the screening. By clicking “Save”, the MoM will be calculated. Moreover, by placing the cursor on the marker’s MoM, a very complete tool tip text about the calculation process with this marker will be displayed, such as the value of the Likelihood Ratio, etc.

Fetal Dichotomous Markers

In this frame we can find all the dichotomous markers for the different trisomies predefined in the current Profile for their assessment. Each one displays a drop-down list on the right with the three possibilities “Yes”, “No” and “Not Assessed (empty)”.

Comments

Free text can be used here to make any comments that may arise concerning the ultrasound screening and ultrasound examination which cannot be included in any other section of this folder.

Risk folder

The aim of this folder is to calculate and display the combined Risk results of the different markers that take part in this process, as well as to allow the direct input (by clicking “Edit”) of the MoM of the biochemical and ultrasound Gaussian markers to calculate the Risks that are used in quality controls like UKNEQAS or the
comparison of the results of this Program with those of other reference programs.

It has seven different frames, which will be dealt with in more detail below, and has the “Calculate”, “Edit”, “Save/Compute”, “Cancel”, “Validate” and “Report” buttons that perform the actions suggested by their labels. Clicking Edit facilitates this function which prepares for the following ones or allows the direct input of the MoM. Clicking Calculate or Save/Compute performs and displays all the Risk calculations with the combination of all the Profile markers used that have been selected with the corresponding check boxes, as long as we have completed all the parameters (weight, correction factors, chromosomopathy history, etc.) that the Administrator defined as obligatory in the configuration program (otherwise informative messages about the missing data appear). Clicking “Validate”, once the data have been saved, confirms that they have been verified by an authorized person and prevents further modification (otherwise it “Devalidates”).

In twin pregnancies with assessed ultrasound markers, the Risks are shown separately for each fetus.

**Gaussian markers**

It displays all the Gaussian markers of the selected Profile (biochemical and ultrasound), with their values, determination date or related biometry, MoM, and single Risks for each marker (this last item depends on the predefined general configuration). By clicking “Edit” and ticking the check box located just below the column called “Manual MoM” we can enter manually the MoM for the markers whose box is checked, as well as the combined Risk calculations of the selected markers by clicking “Calculate”.

Clicking on the symbol located before each marker displays the screen for its edition and modification.
Correction Factors observed

In this section appear, in order, all the correction factors (covariates) defined for the Profile’s screenings with their assessment. Clicking on the symbol located before each one displays the screen for its edition and modification.

Dichotomous Markers

This frame shows, in order, all the dichotomous markers existing in the current Profile with their assessment. Clicking on the symbol located before each one displays the screen for its edition and modification.

Calculated Risks

It displays in graphic and numerical format, depending of the type of screening, the Risks for the patient’s Age, for the different trisomies, the basal risk for Preeclampsia and the Risks for Early and Late Preeclampsia obtained from the combination of all the markers used in the current Profile. The risks for trisomies 21 and 18-13 appear in green when the risk is lower than the predefined cut-off level and in red when it is higher, and the length of the coloured bar is proportional to its value. The maternal age risk and the basal risk for preeclampsia always appear in yellow proportional to their value as it is merely consultative information.

GA Calculation

This box has a drop-down list which allows the selection of the method used to calculate the Gestational Age (GA). By default the value “Auto” is selected, which means that the GA will be calculated using the most reliable parameter entered by the user (the priority is established automatically, in the following descending order: biometry, weeks and days calculated from an ultrasound, conception date and LMP), but we can select manually the method that we want to use: from the Last Menstrual Period (LMP) entered in the corresponding box in the Pregnancy folder; Manually (if the weeks and days of gestation have been entered, on a specific date, in the corresponding box in the Biochemistry folder); using the Conception Date entered in the corresponding box in the Pregnancy folder and, finally, using a Biometry.

This box shows, moreover, a summary of the Gestational Age, the Expected Delivery Date (EDD) and the Maternal Age at the time of the screening.

Comments on the Report

Here we can enter free text comments which, unlike those in the preceding folders, will appear in the printed report in the specific screening for which they are written.

Diagnosis

This small frame has 3 buttons (Edit, Save, and Cancel) as well as a series of drop-down lists (with Yes, No and Not Assessed) corresponding to the different Risks calculated in each specific Profile (for example T21 and T18-13, in a combined first trimester with Risks for T21 and T18-13; EPE and LPE in the case of a
Preeclampsia profile (PE), etc.), for the different fetuses in the case of twin pregnancies. The word “Diagnosis” is shown before theses texts (which correspond with the so-called “Types of screening”, not to be confused with “Types of Screening profile”). Once we have confirmed the Diagnosis of a specific Trisomy or PE (which happens once the screening has been completed), this frame and its buttons can be used to enter, in a very easy way, the confirmation, or not, of the Diagnosis performed by the Screening, and so it will be possible to calculate the Sensitivity, Specificity, False Positive Rate, etc., that is, the real effectiveness of the screening. In any case, and only in the case of aneuploidies, if we complete all the sections of the “Karyotype or Phenotype” box in the “Perinatal Result” folder from the “Post Screening” tab, the different drop-down lists in this “Diagnosis” box will be completed automatically (but not in the Preeclampsia screenings).

Report Button

![Report Button Image]

The function of this button is to generate a Printed Report in PDF format, of the Risk estimation result of the specific screening which is shown in its set of folders.
Post Screening Folders

Selecting the Post Screening tab or folder at the top of the screen (in the Summary Window) displays, on the top right side of the Screening window, the Patients and Pregnancy folders (as in the previous sections) and the following new folders: Invasive Technique, Morphological Ultrasound and Perinatal Result. In the case of twin pregnancies these last three folders will be double, one for each fetus, which was not so in the Screening Folders.

This is a set of three folders whose function is to store a posteriori the information concerning the perinatal result and the complementary or confirmatory techniques that have been made to complement or confirm the result of the screening. Although its completion is not at all necessary for the performance of the screening, it is advisable as a quality control, as it is a good way to know its effectiveness, though not the only one as we mentioned above in the Risk Folder and its “Diagnosis” box, enabling the calculation of the prevalence, the false positive and negatives rates, detection capability, etc.

Invasive Technique Folder

As its name suggests it allows the description of the invasive techniques practised, in general, to confirm or rule out the positive results of the screening.

It has the “Edit”, “Delete”, “Save” and “Cancel” buttons. We click “Edit” to enter data.

It has two sections, the upper one with the description of the invasive technique and the lower one for details of the studies performed with the material obtained from the invasive technique.

In the upper left frame we can enter the following: date of performance of the technique, its identifying code or registration number, the indication, the way of obtaining the sample and the final result (normally the karyotype’s, which exceptionally might not match the result obtained using rapid methods such as FISH or QF-PCR) and even if the patient refuses the technique. In the upper right frame we can enter the unit where the technique is performed and the doctor that performs it. Below this there is a frame for free comment.
The description of the lower section concerning the details of the tests performed includes a check box after the test name, which, if checked, allows the following specifications for each of the tests performed: its result, the centre of performance, its identification code, the date when the result is obtained and an explanatory note if convenient.

**Morphological Ultrasound Folder**

It allows the description of the ultrasound examinations practised during or after the screening.

At the top we find the “Edit”, “Delete”, “Save” and “Cancel” buttons. We press “Edit” to enter data.

In the upper left frame we can enter the date when the ultrasound is performed, the code, register number that identifies it, the definite result and whether the patient refuses the procedure.

In the upper right frame we can select the unit that performs the morphological ultrasound.

In the lower left frame we can select the coded result of the morphological anomalies detected in a such a way that, as these may be multiple, the button [+1] to its right allows us to copy, one by one, each one of those selected from this combo into the text box below, and they can even be eliminated, in case of error, with the button [-].

The frame on the right allows us to add Comments on the morphological ultrasound.

**Perinatal Result Folder**

The final result of a screening process is obtaining one or two fetuses from a process of delivery or abortion, in whom we will confirm or rule out the congenital anomalies detected or suspected in that screening, in the invasive techniques, or in the ultrasounds where the fetal morphology is evaluated. The function of this folder is the systematic registration of all these pieces of information which can be obtained after the expulsion of the fetus from the mother’s womb.

In all twin pregnancies, regardless of chorionicity, two perinatal result folders will be displayed one for each fetus, with the “Edit”, “Delete”, “Save” and “Cancel” buttons.

The folder has eight frames: Birth data, Weight/Gender, Karyotype or Phenotype, Confirmation of perinatal result, Result in
Birth/Abortion, Delivery Unit, Confirmed congenital anomalies and Comments.

The “Birth Data” frame allows the registration of the birth date or Abortion and an identification number of the Newborn Baby.

The Weight / Gender frame allows the description of these fetal characteristics.

In the “Karyotype or Phenotype” frame we can classify the karyotype or phenotype as normal or abnormal and, if abnormal, the different types of aneuploidy can be specified. If we complete this box, the “Diagnosis” section and frame in the “Risk” folder will be automatically completed in the cases of Aneuploidy screening, and so the Sensitivity-Specificity can be calculated in the respective menu, while in the Preeclampsia screenings we must complete the “Diagnosis” box directly in the “Risk” folder, although we can anyway complete the other sections in this Perinatal folder (delivery date, weigh of the newborn, etc.).

In the “Confirmation of perinatal result” frame we can confirm if the screening procedure has been concluded and is considered completed (first three-state drop-down list). We can also confirm if the case is closed, meaning that we have the complete perinatal result (second three-state drop-down list), and finally, in the event of abortion or fetal death, if necropsic study has been practised.

The “Result in Delivery / Abortion” frame allows us to select, by means of drop-down lists, the type of delivery or abortion that the gestation has resulted in.

The Centre or Unit where the delivery took place can be selected from the drop-down list in the “Delivery Unit” frame.

In the “Confirmed Congenital Anomalies” frame we must include the codified result of the morphological anomalies confirmed at birth (which may be different from the ones detected or suspected in the morphological ultrasounds) in such a way that, as these may be multiple, the button [+ ] to its right allows us to copy each one of those selected in this combo, one by one, into the text box below, and they can even be eliminated, in case of error, by means of the [- ] button.

Finally, in the “Comments” section, free text can be used to describe any comments related to the screening perinatal result,
and to its process, which cannot be included in any other section of this folder.

**How to perform a New Screening**

The SsdwLab program you to import directly from an external server, LIS, ultrasound unit, etc., all the necessary parameters to perform a screening. However, the explanations in this user’s guide will only deal with the manual input, accessing the Program by means of a web browser, of the data required for, as an example, an aneuploidy and to generate a report. All the information concerning direct importing from and exporting to other software systems is dealt with in the specific manuals, often personalized for each type of computer system and which as a whole are part of SsdwLab6’s communications protocol based on XML and HL7 language.

To perform a screening on a patient, for a specific pregnancy and in a particular gestational age, we must first configure the screening Profiles that we wish to use and, even though it is not essential, identify the screening program Centres, the laboratories that analyze the blood tests, the ultrasound Units that evaluate the ultrasound markers, the sonographers, etc.

The screening of a patient always starts with the input of all her filiation data in the screen displayed when we press the “Add New Patient” (if she hasn’t been entered in the Program’s database. If she has, we can recuperate her stored data using the button “Patients Search”, and we can also make any modifications using the “Edit” button). The filiation data must include at least Name and Surname, Birth date, and one of the following identifiers: Social Security Number, NIC, PIC and CIC. Although it is not essential, in this screen it is convenient to enter the Race of the patient with the corresponding combo, as it intervenes in the Risk calculations.

Once we have entered the filiation data, we save them using the button with the same name.

If what we want is to perform a “trial” screening (to learn how the Program Works), or to make the calculations corresponding to the External Quality Controls, such as UK NEQAS, we must check the
cheek box “Mark as test”, which allows the performance of all the screening functions that follow, but the records under this mark, and the ones created from them, will not intervene in statistical calculations and in the own quality controls of SsdwLab6 program. It is also advisable to specify with the surname something like: “TRIAL” or “UK NEQAS”, and so they will be easy to select for consultation.

The “Screening” screen displays two horizontal folders, one under the title and one on the top left side, entitled: “Screening data” and “Post-screening data”, for the function expressed by their names. The first one, “Screening Data” is selected by default.

Below these two folders’ tabs we can see the following titles in bold: Patient, Pregnancy, Screening, Blood test, Ultrasound and Risk Calculation. Some folders have a “Delete” button, a Validation “v” button, which allows us to “Validate” the blood test, the ultrasound or the Screening result (in which case the top ribbons in all the frames where their titles are shown change to green and the “Validate” button becomes “Undo Validate”). Finally, the “Risk” folder, which has, among others, the following buttons: “Calculate” (gear icon), “Report” (We can print the Report with the Adobe PDF format icon) and at the right end there is an icon of a Printer that displays, when placing the cursor on it, a list with all the patient’s screening reports issued and the name of the person who performed them.

By selecting the “Patient” folder, we can modify (“Edit”) her administrative data and, for example, add any that we might have forgotten, and finally save them.

The following step in creating a New Screening is opening (with the “Add” button) and complete the data in the “Pregnancy” folder where we can enter the date of the Last Menstrual Period (LMP) which the Program can use for a provisional calculation of the length of gestation (Gestational Age or GA) until we have an Ultrasound Biometry, like CRL, BPD, etc. which are more reliable.

Other important data, but not always required, in this folder are: egg source (own pregnant woman’s or Donor’s, in this case the Donor’s birth date must be entered (with the decimal fraction of the months) at estimated birth date, as this age will be used for the important calculation of Maternal Age Risk; the pregnancy type (spontaneous, IVF, etc.), if it is a Single (by default) or Double gestation, and in this case the placental type (mono or dichorionic) must be entered as it influences the Risk calculations; the mother’s weight (the most important correction factor for biochemistry) at screening time (height is not used in the Trisomy Risk calculations and it is only useful for the calculation of the BMI (Body Mass Index) which will be used in the calculation of the risk for preeclampsia, and the Smoking Habit, in number of cigarettes/day, which is another important correction factor for biochemistry.

The remaining parameters are not used in Risk calculations and their recording is only from an epidemiological point of view (their display depends on the general configuration. At this point, the data must be saved with the corresponding button and in the
combo displayed next to the name of the folder, “1” will be shown meaning that there is 1 Pregnancy from this patient (2 or more if there existed previous gestations from her).

The next step in creating a New Screening is opening (with the button “Add”) and completing the data in the “Screening” folder where at least, we must enter the Screening Date (usually the date when the blood sample was drawn for the biochemistry) and select the type of Profile to be used for this screening (combined of first trimester, double test of second trimester, Preeclampsia, etc.) in the respective combo. The remaining data aren’t always obligatory, but among them it is important to complete “Centre” (it usually appears by default), the 3 concerning the Acceptance of the Screening (which may be obligatory in some Centres), the antecedents of previous Congenital Anomalies, the ones for the correction factors that have not been completed automatically when entering them in the previous folders (like Race in the folder of the patient’s administrative data or Smoking in the Pregnancy folder), and finally the Requesting Doctor and the Screening Report Signatory.

In the Risk for Preeclampsia screenings we must enter the Dichotomous Markers for Maternal Antecedents (they vary depending on the configuration of the Screening Profile) which act modifying the Basal Risk and the Risk for Early and Late Preeclampsia (EPE and LPE), and the values of the measurements of Maternal Blood Pressure.

At this point, the data must be saved with the corresponding button and in the present combo right next to the name of the folder, “1” will appear meaning that there is 1 Screening from this patient (2 or more if there existed previous screenings from her), so it is convenient to Save and exit the “Screening” folder for a better view of the whole screen.

The next step to make a Screening is to open (with the “Edit” button) and fill in the data in the “Blood test” folder, where the Screening date is the same as the one in the “Screening” folder, which can obviously be modified, and enter the values of the biochemical markers. The remaining data in this folder are optional, and particularly the Laboratory occurs automatically.

This folder has the Validation button to its right (depending on how it is defined in the general Configuration) and by clicking on it we validate the biochemistry (it changes to green the ribbons corresponding to the frame titles).

The next step to perform a New Screening consists in opening (with the “Edit” button) and completing the information from the “Ultrasound” folder where we can find the Date when the ultrasound was performed (it has the current day’s date by default) which can be modified, the “Biometry” frame which contains the biometries that can be used for the calculation of the Gestational Age for the Screening Profile that is being used. We must complete one of these biometries, and tick the check box on its left, so that it is used for the calculation of the Gestational Age (GA), and the “Gaussian Ultrasound Markers” frame which allows
you to enter the Nuchal Translucency or other previously defined markers in the first trimester screenings.

Depending on the type of screening, and on the configuration of its Profile, the frame with the Fetal Dichotomous Markers for the different trisomies will be displayed and, if we want to use them for the Risk calculations, we must complete the corresponding drop-down lists with Yes or No.

On the top right side of this folder we can enter or select the Ultrasound Code and unit and the name of the Sonographer, which is only required when the identification of the sonographer (who must be accredited) has been defined as obligatory in the Profile (General folder in the Profiles Administrator submenu in the “Administration” menu).

When we click the “Save” button, the MoM, the partial Likelihood Ratios, etc. are automatically calculated and shown in tool tip text which is displayed when we place the cursor over each marker. Depending on the General Configuration of the Program this folder can also have the “Validate” button, which functions as in the “Blood Test” folder.

When the Program has enough information to calculate the Combined Risk for all the markers used in the Screening Profile and all the Secondary Risks (also defined in the Screening Profile), they will be displayed both in the Summary window and in the “Risk” folder in the Screening window. We can perform the same function manually by clicking on the “Calculate” button in the “Risk” folder.

The Total and significant Risks (for the different trisomies and/or early and late preeclampsia) are shown in numerical and graphic format with a circle and a segment, both green if there is no Risk or red if there is (in this case the length of the red segment will be proportional to the Risk. The Secondary Risks (Maternal Age in trisomies or Basal in the preeclampsia) are shown with a grey circle and a yellow segment, also proportional to the Risk.

This folder is highly informative and shows a summary of the markers concerned with the Risk calculation of the specific patient with the respective MoM, corrected and uncorrected by the correction factors, as well as the Likelihood Ratio and the partial Risks for each Marker, etc., which are shown in a tooltip text that is displayed when we place the cursor over each marker.
When we click the button with Adobe PDF icon, the Screening Report is displayed on the screen in the established format, which can either be saved or printed. In the text box called “Report Comments” we can enter contents that will appear in the printed report in this particular Screening. By clicking on the “Validate” button we protect the screening data from further modification unless we click on “Invalidate” (which requires special permissions) which is displayed alternately with “Validate”.

This folder allows, moreover, the manual input of the MoM for one or more Gaussian markers, having previously ticked the corresponding check boxes called “Manual MoM”. This is specially useful in the quality controls by different institutions, like UKNEQAS, the rest of the calculation procedure being identical although, in the case of quality control it is advisable to tick the check box called “Mark as test” in the folder of Identification Data of the Selected Patient as this way these records are not used for the statistical calculations and quality controls that the SsdwLab6 program itself carries out with its own screening records.

How to perform a Twin Screening

The programs of SsdwLab series deal with twin gestations in a special way, different from most other software aimed at the detection of aneuploidy, which just divide the MoM of the biochemical markers by a correction factor (around 2) and give little importance, if any, to chorionicity.

In pregnancies with more than one fetus, the biochemical markers, determined in maternal serum, come from the multiple fetuses and placentas; unlike fetal-specific ultrasound markers, such as NT, where they are evaluated individually in each one of them.

A twin pregnancy cannot be treated like a correction factor, or a covariable, that corrects the MoM. This is because when we apply a correction factor on the MoM we assume that its effect on the MoM doesn’t differ depending on whether the gestations are affected or unaffected, which is false, especially in dizygotic gestations (the most frequent ones), where, normally, only one fetus will be affected. So, it is necessary to use specific serological population parameters, while for the anatomic or functional fetal ultrasound markers, fetal-specific, it will not be necessary.
Chorionicity can be determined with high accuracy by using the first trimester ultrasound, and it is closely related to zygosity; in such a way that all monochorionic twins are monozygotic and 85-90% of the dichorionic are dizygotic.

Nowadays, in the absence of better data, it is assumed that the risk a priori for the gestational age does not differ depending on whether it is a twin or single pregnancy.

In aneuploidy unaffected gestations, the average levels of the biochemical markers is approximately twice their average in single gestations, while the standard deviation and the correlation coefficients there is practically no difference.

In the gestations with one or two trisomy 21 or 18 affected fetuses, the population parameters (median, standard deviation and correlation coefficients) cannot be estimated directly, due to the lack of sufficiently large series.

All the above arguments, supported by an extensive literature, bring us to the conclusion that we need to deal with twin gestations in a way different from the way we approach single gestations; and to the pseudo-risk concept when we calculate a single risk for a twin gestation, which will be necessary whenever we are not using at least one anatomic or functional fetal ultrasound marker (fetal-specific) such as NT.

When using the method implemented in SsdwLab5 (with its own population parameters) the Profile’s characteristic and settings are as follows:

The median (log 10 MoM) for monochorionic and dichorionic twin pregnancies unaffected by aneuploidy in the second trimester, have been taken from a meta-analysis by Cuckle in 1998. For those in the first trimester, we have used Spencer’s publication in 2000.

The median (log 10 MoM) for aneuploidy affected monochorionic twin pregnancies is estimated by multiplying the median calculated for affected fetuses in a single gestation by the median of unaffected twin gestations, and converting the result into its decimal logarithm.
In aneuploidy affected dichorionic gestations it is assumed that, most probably, only one of the fetuses will be affected, and that both contribute proportionally to the concentration of the marker in the maternal serum, so we must multiply the median of unaffected twin pregnancies by the addition of the median calculated for the affected fetuses in a single gestation plus the median calculated for the unaffected fetuses in a single gestation divided by 2, and converting the result into its decimal logarithm.

We use the standard deviations and the correlation coefficients corresponding to the single gestations because, as already mentioned, they do not show significant differences from the twin gestations.

When using an anatomic or functional fetal ultrasound marker (fetal-specific) like NT, in monochorionic gestations, we must decide if we use the smaller CRL and the largest NT, the largest CRL and the median of the NT, (according the latest publications: Screening for trisomy 21 in twin pregnancies in the first trimester: an update of the impact of chorionicity on maternal serum markers. Spencer K, Kagan KO, Nicolaides KH. Prenat Diagn. 2008 Jan; 28(1):49-52 and Screening for trisomy 21 in monochorionic twins by measurement of fetal nuchal translucency thickness. Vandecruys H, Faiola S, Auer M, Sebire N, Nicolaides KH. Ultrasound Obstet Gynecol. 2005 Jun; 25(6):551-3), the arithmetic mean of both, or the geometric mean of the NT, as Wald suggests, since it is the one that has a more Gaussian distribution, and estimate a single pseudo-risk, called “pregnancy-specific pseudo-risk” rather than “fetus-specific pseudo-risk” (Wald 2003 method for twins), whereas in dichorionic gestations it is highly advisable to calculate the risk corresponding to each fetus individualized from its CRL and NT.

It must be noted that, in the so-called SsdwLab5 (own population parameters) for the Risk calculation for Twins, the MoM that the
SsdwLab6 program calculates for the biochemical markers of twin gestations (serological markers of maternal or fetal origin) do not really represent those of a twin gestation, but the equivalent to a single fetus gestation, so in the MoMs we should mentally divide by 2 in order to have a realistic approximation to the participation of each fetus. On the other hand, when we use the so-called Wald 1991 Methods (modified for chorionicity) and Wald 2003, the MoM calculated and displayed have in fact been divided by a specific, normally different, factor in monochorionic and dichorionic twins. The different methods in SsdwLab6 for Risk calculation in Twins are predetermined, for each Screening Profile, in their configuration.

New evidences in Twins

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<thead>
<tr>
<th>Study</th>
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<th>Dichorionic</th>
<th>All</th>
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<td>Free beta hCG</td>
<td>1.53</td>
<td>2.11</td>
<td>1.99</td>
</tr>
</tbody>
</table>

After this broad theoretical introduction, which we believe necessary for a correct understanding of how the program calculates the Risk in double gestations, the creation of a New Screening for a Twin Pregnancy is performed as we did for a single pregnancy (and explained in the previous section “How to perform a New Screening”) up to the Pregnancy folder where, as described, we must select “2” in the corresponding combo and then select the chorionicity option (Monochorionic, Dichorionic or Not Assessed, and in this last case the Program will consider the gestation as if it were Dichorionic, as it is the most common type).

At this point, in the case of specific fetal parameters and markers such as the biometries, the NT or the fetal dichotomous markers, the program will display, in the following folders, a control for the input, or selection, of the mentioned parameters and markers for each fetus, with the Fetus 1 and Fetus 2 texts respectively.

We must remember that in twin gestations (mono and dichorionic) with Screening Profiles without Ultrasound Markers (normally second trimester screenings) the Biochemical Markers will be common to both fetuses and the Risk Estimate will also be common for both fetuses (gestation pseudo-risk) just as the screening Report, whereas the monochorionic double gestations with a Screening Profile that includes Ultrasound Markers (normally first trimester) will behave as the ones that do not include those markers as regards the Biochemistry, the Ultrasound, the Risk Calculation and the Report (all shared by both fetuses) and finally in the dichorionic double gestations with Ultrasound Markers we must fill in a check box, a text box or a drop-down list for each fetus, and the Risk Calculation, specific for each fetus, will be performed and printed.
In all double gestations, mono and dichorionic and with any type of Profile, the Post-Screening Data tab will display the “Invasive Techniques”, “Morphological Ultrasound” and “Perinatal Result” folders will be double and specific for each fetus and they will have to be completed as such.

“Search” menu

At the top of the program’s screen a menu there is a menu bar. The first menu is called Search and it is accessible to almost all users with Edition permission.

This menu has the following 3 submenus (all 3 with the same characteristic type of display regarding table format and selection filters): Patients Search, Screening Search and Post-Screening data Search.

Patients Search

The screen that is shown when we access this submenu is the same that was described in the section “Patients Administration (and Screenings)” which is presented at the beginning of the Program, so its description will be obviated here. As its name suggests, it allows all the actions related to search, queries, modification and entries.

Screening Search

This is a very useful screen for the consultation of the screenings performed on the different patients. It displays in table format, in synthesized and graphic form, the most relevant data of each screening, including age Risks, the Trisomies and Preeclampsia. Moreover, it allows you to view the selected screenings.

The screenings that will be displayed on the screen can be selected by means of the multiple filters that are shown in the column on the left of the screen and we can organise their display from multiple fields in an ascending or descending form. The selection filters include a range of dates, the Screening units, the Profile, whether the Risk has been Calculated, Validated or is pending Recalculation, include or exclude the patients marked as “test” or those whose screening has been “suspended”, as well as the patient’s identification, NIC, CIC and Name and Surname. Moreover, a series of grey drop-down lists are shown at the bottom of the window on the left that widen the selection with the most common parameters in the screening folders (Patient, Pregnancy, Screening, Blood Test, Ultrasound and Gestational Age).
All text type filters (text box with check box and combo “*a*”) allow, with the selection of the combo items, the following types of search: “*a*” which finds the coincidences with the entered text when it is within the searched text; “a*” which finds the coincidences with the entered text when it is at the beginning of the searched text; “*a” which finds the coincidences with the entered text when this is at the end of the searched text, and “!a*” which finds the differences with the searched text.

**Post-Screening Data Search**

This screen is similar to the one above but this one displays, in table form, the patients on whom a Screening has been performed and who have data in the Post-Screening folder and windows.

The selection filters include a range of dates and the most common parameters for each one of the options displayed in grey at the bottom of the window on the left (Patient, Pregnancy, Invasive Techniques, Morphological Ultrasound and Perinatal Result), as well as for the patient’s identifiers.

All text type filters (text box with check box and combo “*a*”) allow, with the selection of the combo items, the following types of search: “*a*” which finds the coincidences with the entered text when it is within the searched text; “a*” which finds the coincidences with the entered text when it is at the beginning of the searched text; “*a” which finds the coincidences with the entered text when this is at the end of the searched text, and “!a*” which finds the differences with the searched text.

**“Tools” menu**

It is the second menu on the top Menu bar and includes a series of functions for record Search, Advanced searches, Quality Controls, Automatic Calculations (Correction Factors and Correlation Coefficients), Statistics (Population Parameters Distribution) and Validation of biochemical analysis.
Access to the different submenus depends on the privileges of each individual user, some of them being reserved exclusively for the Administrators.

**Quality Controls**

This submenu displays 4 new submenus for performing the following specific quality controls; Percentage of positive cases, Median MoM (which in turn displays 4 new submenus: Temporal trends, According to gestational age, According to maternal weight and According to correction factors), Sensitivity-Specificity and CUSUM for the Blood Test and for the Ultrasound. Quality controls are very important tools to learn how to develop the population screening program and when the indicators are not optimum, to know what adjustments must be made.

**Percentage of positive cases (PCP)**

It is not always possible to determine the False Positive Rate (FPR) or their percentage since this requires knowledge of the perinatal results of all those screening tests carried out. As the positive cases are not very frequent, a good approximation of the FPR is the percentage of positive cases (PPC). This is a very useful parameter in order to find out the quality of the screening method being used, since there are numerous papers published which describe the perspective FPR for a certain patient age distribution, evaluated from its mean and standard deviation.

We believe that it can be very safely stated that knowledge of the PPC (when it is not possible to know the FPR) and of the median of the Multiples of the Median (MoM) for each marker used constitutes the best parameters for setting the quality level of a screening program. There are also good indicators of the need to make modifications on it when they are not at desirable intervals, which can be detected with a relatively low number of screening tests. On the other hand, when the screening program is applied and it works well, the detection rate or sensitivity will always be related to the PPC and to the studied patients’ age distribution.
This screen allows us to select (filter) the screenings that will be included in the query, which means that they will be selected for the calculations. So we can choose from a range of dates, from what Centres, if only Validated cases are included, include only one range of patients’ ages, from which Profiles, Risk type (the different trisomies, NTD and preeclampsia and whether we evaluate the Risk only for single-fetus gestations or for twin gestations and the confidence interval (95 or 99%) admitted. If the selection of dates allows it, a presentation organized monthly along a year is made and in all cases based on the total number of selected records.

All the previous controls are located in the left sub-panel which has a button at the top named “Execute Query” which performs this function though this is normally done automatically a few moments after the input of the conditions.

The right sub-panel appears in two parts, an upper and a lower one. The lower part displays the results in chart or table format, as selected, with some dots that situate the PCP monthly, each one of them with two horizontal lines, an upper one and a lower one that represent respectively the higher and the lower levels in the confidence interval. The upper part of this sub-panel shows, on the left, the overall results (without monthly distribution) and on the right a summary of the filters applied to the selection and above the first column there are a series of buttons under the “Generate PDF” title, whose function is to display a complete printable report in PDF format, “Export Image” and “Export List” with the functions that their names suggest.

**Median of the MoM**

One of the main quality criteria of the methodology and correction in the screening risk calculations is that the median of the Multiples of the Median (MoM) of a certain marker must be located as close to 1 as possible. This module allows to calculate this parameter easily (the median is the 50\textsuperscript{th} percentile). It is very important to be
able to display the uncorrected MoM simultaneously with the MoM corrected by the different corrective factors used, since in this way the influence of these over the values distribution of the marker MoM can be observed.

This submenu shows the Median of the Multiple of the Median (MoM) based on these different criteria: Temporal trends, According to gestational age, According to maternal weight and According to correction factors.

**Median MoM. Temporal trends**

This option shows the median of the MoM of a Gaussian marker in a monthly display, when the selection of dates makes it possible, and globally from all selected records. It displays the MoM “corrected” by the different correction factors (maternal weight, race, diabetes, etc.) in green and the “uncorrected” ones are displayed in grey in the charts.

This screen allows us to select (filter) the screenings that will be included in the query, which means that they will be selected for the calculations. So we can choose from a range of dates, from which Centres, whether only Validated cases are included and we can limit the number of months to be included. As specific filters of the Gaussian Marker we must select the one we are analyzing and the Profile it belongs to, the number of fetuses in this gestation and the limits on the value of the MoM beyond which they will not be included in the calculations (as these results could be erroneous). We can also select the Biochemical Laboratory that we wish to evaluate if it is a biochemical marker (by means of the corresponding check box and the selection combo), or in the case of a Gaussian ultrasound marker, like NT, we can filter through Ultrasound Unit or even through Sonographer, in this last case by marking the corresponding check box and selecting both the Unit and the Sonographer combos.

This screen also displays the so called “Special Filters” that allow the selection by the different correction factors existing in the
selected Screening Profile, the ones that affect the patient’s demographic data in simple drop-down lists, and the ones that affect the screening itself by means of a check box, a drop-down list that includes or excludes them and a second drop-down list to “accept”, “refuse” or “without information” regarding their inclusion or exclusion.

The Begin event and End event drop-down lists allow you to select the data registered between two Temporal events which have been previously defined, by means of the “Temporal events” submenu in the Administration menu.

All the previous controls are located in the left sub-panel which has a button at the top named “Make Query” which performs this function though this is normally done automatically a few moments after the input of the conditions.

The right sub-panel has two parts, an upper one and a lower one. The lower part displays the results in chart or table format, as selected, with some dots that situate the Mom monthly (green for the corrected MoM and grey for the uncorrected ones), each one of them with two horizontal lines, an upper one and a lower one that represent respectively the higher and the lower levels in the 95% confidence interval. The upper part of this sub-panel shows, on the left, the overall results column (without monthly distribution) and on the right a summary of the filters applied to the selection, while above the first column there are three buttons called “Generate PDF”, whose function is to display a complete printable report in PDF format, “Export Image” and “Export List”, with the functions that their names suggest.

We must remember that the closer to the line of 1 the "corrected" and "uncorrected" MoM results are, the better the quality of the screening will be, and that beyond the green zone (±10%) remedial measures must be implemented.

**Median MoM. According to gestational age**

This option shows the median of the MoM of a Gaussian marker according to gestational age in a weekly display when dealing with a biochemical marker and in a biometric display (normally CRL intervals) when dealing with an ultrasound marker. It displays the MoM corrected by the different correction factors (maternal age, race, diabetes, etc.) in green and the “uncorrected” ones are displayed in grey in the charts.
This screen allows us to select (filter) the screenings that will be included in the query, that is, that they will be selected for the calculations. So we can choose from a range of dates, from which Centres, whether only Validated cases are included, limit the number of months that will be included, and as specific filters of the Gaussian Marker we must select the one we are analyzing and the Profile it belongs to, the number of fetuses in this gestation and the limits on the value of the MoM beyond which they will not be included in the calculations (as these results could be erroneous). We can also select the Biochemical Laboratory that we wish to evaluate/assess if it is a biochemical marker (by means of the corresponding check box and the selection combo), or in the case of a Gaussian ultrasound marker, like NT, we can filter through Ultrasound Unit or even through Sonographer, in that one, by checking the corresponding check box and selecting both the Unit and the Sonographer combos.

This screen also displays the so called “Special Filters” that allow the selection by the different correction factors existing in the selected Screening Profile, the ones that affect the patient’s demographic data in simple drop-down lists, and the ones that affect the screening itself by means of a check box, a drop-down list that includes or excludes them and a second drop-down list to “accept,” “refuse” or “without information” regarding their inclusion or exclusion.

The Begin event and End event drop-down lists allow you to select the data registered between two Temporal events which have been previously defined, by means of the “Temporal events” submenu in the Administration menu.

All the previous controls are located in the left sub-panel which also has a button at the top named “Make Query” which performs this function though this is normally done automatically a few moments after the input of the conditions.

The right sub-panel has two parts, an upper one and a lower one. The lower part displays the results in chart or table format, as selected, with some dots that situate the MoM monthly (green for the corrected MoM and grey for the uncorrected ones), each one
of them with two horizontal lines, an upper one and a lower one that represent respectively the higher and the lower levels in the 95% confidence interval. The upper part of this sub-panel shows, on the left, the column with the overall results (without monthly distribution) and on the right a summary of the filters applied to the selection, while above the first column there are three buttons called “Generate PDF”, whose function is to display a complete printable report in PDF format, “Export Image” and “Export List”, with the functions of the same name.

We must insist and remember that the more the results (“corrected” and “uncorrected”) approach the 1MoM line, the better the quality of the screening will be, and that outside the green zone (± 10%), correcting measures must be implemented.

**Median MoM. According to maternal weight**

This option, identical to the previously mentioned one, regarding the selection criteria, shows the median of the MoM of a Gaussian Marker distributed according to maternal weight at intervals of 10 kg. Moreover, it displays the MoM “corrected” by the different correction factors (maternal weight, race, diabetes, etc.) in green and the “uncorrected” ones are displayed in grey in the charts.

**Median MoM. According to correction factors**

This option, totally identical to the previously mentioned one, regarding the selection criteria except for the fact that we must select the “Correction Factor” that we wish to assess, displays the median of the MoM of a Gaussian Marker distributed according to each of the different correction factors of the Profile and marker, no matter whether they are present or absent.
Sensitivity-Specificity

This option allows the automatic or manual calculation of the effectiveness of a “Diagnostic or Screening Method”, from the respective frequencies viewed or entered in a contingency table with two columns by two rows (Abnormal Result, Normal Result, Positive Risk and Negative Risk). This requires having done a complete follow-up of all the screenings up to birth or abortion. We must also have classified correctly the products of the pregnancy as normal regarding karyotype or phenotype, and what type of aneuploidy they present in the Perinatal Result folder, or else we must have completed the “Diagnosis” section in the “Risk” folder, which allows us to confirm or deny the accuracy of the result offered by the screening in relation to the result obtained at term in a more simple way, and the only possible way in the cases of screening for preeclampsia.

Automatic calculation takes the data of Positive (aneuploidy of different types depending on the selection made) and Negative (normal karyotype or phenotype) cases from the Perinatal Result folder, specifically from the “Karyotype or Phenotype” frame which has different option buttons and a drop-down list allowing us to classify all types of aneuploidy or on the other hand to define a fetus with a normal karyotype or phenotype. As regards Risk, it sets as Positive Risk all the ones whose calculation is above the selected level, whereas the other ones are considered as Negative Risk. In preeclampsia, as has just been mentioned, we only have to enter the Post-Screening information in the “Diagnosis” section of the “Risk” folder, while for the aneuploidies either of the two possibilities may be used, as the first one (Post-Screening folder) automatically updates the last one (Diagnosis).
The following parameters are calculated and displayed: Sensitivity (Detection Rate), Specificity, Predictive Positive Value, Predictive Negative Value, Efficiency, Prevalence, False Positive Rate, False Negative Rate, Likelihood Ratio when the test is positive, Likelihood Ratio when the test is negative, and the respective 95% or 99% Confidence Intervals, depending on the one we select (CI 95%-99%), the value of the Chi Square and of the Odds-Ratio (an approach to the Relative Risk) with the limits for the Confidence Interval according to Taylor, Wolf, and Meittinen's methods.

This screen allows us to select (filter) the screenings that will be included in the queries and set the cut-off limits in the Risk. So we can select from a range of dates, the Screening Profile, from which Centres, whether only Validated cases are included, or only closed Cases, the type of aneuploidy, NTD or preeclampsia and single or twin pregnancy. Moreover, we can select the Confidence Interval to be calculated at 95% or 99%. When we select the “Manual Entry” check box, the text boxes below are activated and allow the manual input of the data in the respective cells in the contingency table (2x2), and the existing data in the Program’s database are not assessed.

The right sub-panel displays, from top to bottom, the contingency table (2x2), the result of all the calculations performed. Its upper part displays the column with the overall results on the left and a summary of the filters applied to the selection on the right, whereas above the first column there is a button named “Generate PDF” whose function is to present a complete report and print it in PDF format.

CUSUM

Among the quality controls of the screening markers based on the distribution of the determinations, the CUSUM method is the only one to offer a prospective method. This involves a number of advantages in comparison with other methods based on distribution (i.e. the median of the MoMs) such as a bigger precocity in the detection of deviations and a bigger independence from the number of determinations performed during the period.
CUSUM score

- Accumulated sum of the deviations between the measurements and the reference values
- Monitors the mean of the process and detects small deviations
- $\Delta NT = \text{observed value - expected value (median)}$
- Gaussian distribution of $\Delta NT$ with mean $= 0$ y $SD = \sigma (0,25)$
- $K$ is the reference value and is taken as $0,5$ g ($g =$ number of SD to detect $= 0,5 \pm 2$)
- $H$ are the superior and inferior limits ($5 - 40$ SD)
- The CUSUM+ or superior and CUSUM- or inferior is estimated

$C_i^+ = \max [0, \Delta TN_i - K + C_{i-1}^+]$ y $C_i^- = \max [0, -K- \Delta TN_i + C_{i-1}^-]$

The CUSUM graphic method, which among the quality control methods is especially useful for the detection of small deviations, is based on the cumulative sum of the deviations between the observed and the expected measurements. In the specific case of the markers, the expected value is the reference value for the specific gestational age in which it was determined (1 MoM or, which the same, 0 Log 10 MoM is). If the distribution of the different measurements of a marker is correct, the values of these measurements are higher or lower than the expected ones following a known and symmetric distribution, so the cumulative sum of the deviations tend to zero. On the other hand, if the measurements show a deviation, the cumulative sum of the deviations will increase in a positive sense if the deviation is in positive or in the negative sense if the deviation is in negative. The main parameter to establish in order to calculate the CUSUM is the deviation that we wish to detect (establishing the specific deviation in MoMs by means of which the $K+$ and $K-$ parameters, which depend directly on this deviation, are calculated). The remaining parameters used in the calculation of the CUSUM are the ones corresponding to the known distribution of the marker that we wish to evaluate.

The other advantage of this method is that it can be represented in graphic form to make interpretation easier. There are different ways of representing the CUSUM graphically; in SsdwLab6 we have chosen the “decision interval” representation due to its ease of interpretation. This representation consists of two lines for the CUSUM value that change along with the successive determinations, one on the positive side of the Y axis which monitorizes the positive deviations (overestimations) and another line on the negative side of the Y axis which monitorizes the negative deviations (infraestimations). Moreover, there are two limit lines in the Y axis (higher limit or $H+$ and lower limit or $H-$). If the distribution of the measurements corresponds with the expected distribution, both lines of the CUSUM oscillate away from the basal line and back towards it (Figure 1). If there is an
overestimation, the positive CUSUM line moves progressively apart from the basal line until it crosses over the positive limit (Figure 2). If, on the other hand, there is an infraestimation, the line of the negative CUSUM will move apart from the basal line and reach the negative limit (Figure 3).

Figure 1: Correct distribution of the determinations

![Figure 1](image1.png)

**Figure 2: Overestimation**

![Figure 2](image2.png)

**Figure 3: Infraestimation**

![Figure 3](image3.png)

We have to take into consideration that this method detects the tendency towards deviation, this is why, for small deviations, it is normal that the CUSUM reaches the corresponding limit before the deviation that we wish to detect has actually taken place. Likewise, since it is a statistical method, false alarms may occur. In this respect, we can decrease the $H^{+}$ and $H^{-}$ limits, so increasing the precocity in the detection of deviations but at the expense of also increasing the probability of false alarms. For the deviation of 0.1 MoM, taking into consideration the distribution of the normally used markers, by placing the limits in the values +/- 15, that’s the predefined value in SsdwLab5, we get a good balance between precocity of detection and the presence of false alarms. The “within-range” option allows you to limit even more the false alarms, as it accepts the range of half of the deviation to be
detected as a normal value. Figure 4 shows the typical form of a false alarm.

Figure 4: False alarm

An important aspect when we have to calculate the CUSUM for the markers used in the screening, whose basic function is limiting the presence of false alarms, is limiting the values of the markers. This limitation can be carried out in two different ways:

One first limitation that we can apply is the truncation of the MoM. The probability distribution of the Log10 MoM follows a normal distribution in a specific range of MoM, outside this range (at both ends) the distribution moves away from the normal distribution. For this reason, as in the risk calculation, the values outside the acceptable range of normality of the PAPP-A is between 0.2 and 3 MoMs, a value of 0.1 MoMs would be computed as 0.2 MoMs in the calculations and a value of 7 MoMs would be computed as 3 MoM in the calculations.

The second limitation that we can apply is excluding a marker’s extreme values from the graphic, those outside a range of real values of the measurement, established for each marker. This limitation, which can also be applied to other quality control parameters, is due to the fact that quality controls are based on the distribution of measurements of normal fetuses (as in practically all cases), but occasionally there is the case of a fetus with extreme values in some marker, either due to a chromosomopathy or for other causes (for example a cardiopathy in the ultrasound markers or placental insufficiency in the biochemical markers). In order to prevent these very extreme values to cause such an important deviation in the CUSUM that would directly reach the limits, we exclude from the graphic the values of the markers outside the defined range. This limitation is situated between 0.1 and 4 mm in the case of nuchal translucency, and between 0.1 and 3 for the Ductus venosus pulsatility index, but these limits are not well defined in the case of the biochemical markers.

CUSUM Biochemistry

The CUSUM or Cumulative Sum of Deviations between the Observed and Expected values monitors the mean of a process and detects small deviations. It is quite a common way to control the quality of a process in industry and it has only recently been applied in the control and evaluation of the quality of the
biochemistry and ultrasound markers such as Nuchal Translucency.

This option allows the evaluation of the CUSUM for a biochemical marker based on the knowledge of its MoM.

In the left sub-panel we can select, from top to bottom, between which dates the calculations are going to be performed, the validation or not of the screenings, the Screening Profile, the Gaussian Biochemical Marker on which the evaluation is going to be performed, the Type of Screening analysed, the limits in its respective units, among which the following will be evaluated: the MoM type (corrected or uncorrected for the maternal weight and the remaining correction factors), the number of fetuses, the (Log10(MoM) calculation method, whether or not we use the Within Range methodology which allows you to limit the false alarms as it accepts as normal the range of half the deviation that we want to detect, the K+ and K-constants, which are the reference values that are normally taken as 0.5 g (where “g” is the number of standard deviations to be detected, which usually take a value between 0.5 and 2), and the Blood Test Unit that is going to be evaluated.

The Begin event and End event drop-down lists allow you to select the data registered between two Temporal events which have been previously defined, by means of the “Temporal events” submenu in the Administration menu.

The top section of the right sub-panel has two different parts: the one on the left which allows you to select what will be viewed on the X-axis (usually Number of Samples), and the upper and lower limits of the CUSUM in the Y-axis, which is normally set between 5 and 40 standard deviations, typically 0.25; and on the right side we find the data of the laboratory that we are evaluating.

The bottom section of the right sub-panel shows the CUSUM graph which will be assessed as possibly adequate when it does not exceed the upper or lower limits of the CUSUM and the more it
approaches the "0" midline the better. It will be assessed as inadequate when the graph exceeds the limits mentioned.

The "Generate PDF", "Export Image" and "Export List" buttons have the same functions as in the other tools, while the icon with the spanner displays the name of laboratory with the number of samples, the median of the MoM and its standard deviation.

CUSUM Ultrasound

This option allows the evaluation of the CUSUM for a Gaussian Ultrasound Marker (such as the NT) for each one of the explorers (sonographers) of an Ultrasound Unit.

In the left sub-panel we can select, from top to bottom, between which dates the calculations are going to be performed, the validation or not of the screenings, the Screening Profile, the Gaussian Ultrasound Marker on which the evaluation is going to be performed, the Type of Screening analysed, the limits expressed in mm between which the evaluation will be carried out, the number of fetuses, the (Log10(MoM) calculation method, whether or not we use the Within Range methodology which allows you to limit the false alarms as it accepts as normal the range of half of the deviation that we want to detect, the K+ and K-constants which are the reference values that are normally taken as 0.5g (where "g" is the number of standard deviations to be detected, which usually take a value between 0.5 and 2), and the Blood Test Unit that is going to be evaluated.

The Begin event and End event drop-down lists allow you to select the data registered between two Temporal events which have been previously defined, by means of the “Temporal events” submenu in the Administration menu.

The top right sub-panel has two different parts: the one on the left which allows you to select what will be viewed on the X-axis (usually the Sample Number), and the lower and upper limits of the CUSUM on the Y-axis, which is normally set between 5 and 40 standard deviations, typically 0.25; On the right side of this sub-panel we find a list with the available sonographers, with a check box before the identification of each one, which (if checked)
displays their results in the graph. Next to each one, the number of samples that are evaluated is displayed, as well as the median of the deviations from the expected value and their standard deviation.

The bottom section of the right sub-panel shows the CUSUM graph, where we can assess the quality of the ultrasound screening as adequate, provided that a sonographer’s graph does not exceed the upper or lower limits of the CUSUM, and the more it approaches the “0” midline the better. It will be assessed as inadequate when the graph exceeds the limits mentioned.

The “Generate PDF”, “Export Image” and “Export List” buttons have the same functions as in the other tools, while the icon with the spanner displays the list of sonographers with the details of their screenings.

**Automatic Calculations**

This submenu displays 4 new submenus for the performance of the following automated calculations made from the screenings database: Calculations of medians and regression coefficients, Calculations of the weight correction coefficients, Calculation of predefined correction factors, and Calculation of population parameters which in turn includes 2 submenus: Gauss Curve and Correlation Coefficients.

**Calculation of median and Regression coefficients**

The Multiples of the Median (MoM) for each marker are calculated by dividing their real value by that of the corresponding median at the same gestational time (day for the biochemical ones and mm for the biometry selected in the ultrasound ones). The values of the median of a Marker for the gestational time or biometry are obtained from a regression function derived from both measures, being weighed for the number of determinations available at each point or for each biometry interval of the gestation (weighting increases the regression precision at its extremes, that is at those points where a smaller number of determinations is usually available).
This option facilitates the completely automatic calculation of the medians of the marker for every week or biometry interval of the gestation and the regression function coefficients already calculated from patient screening tests data. It is therefore advisable to have a minimum of 100 samples (patients) for gestational moment or biometry in the habitual interval for the type of screening test that is being carried out.

The advantages of using the screening experience itself are obvious and have been highlighted in the various publications on the topic. This way, when we have large numbers of screening tests it is highly advisable to use them to determine the medians with the coefficients of the regression function that represents them, maternal weight correction and other correction factors (covariables), etc. and apply it to the successive patients, so that their screening tests become much more reliable.

This is a fairly complex screen divided into two panels: the left one and the right one which, in turn, is divided into two (upper and lower) sub-panels.

In the left panel, from top to bottom, we first find the button “Execute Query” which is used to run the process of this option once all the conditions (filters) have been entered, although in most cases we will not need to press it as it will be run automatically as soon as we have finished entering the conditions.
Below the “Make Query” button, we find the first controls grouped under the heading “Gaussian Marker”, which are used to select the Marker, for which we are going to calculate the regression function of its medians, which is part of a screening Profile, which we must select previously, as well as the limits within which the data corresponding to the ordinates (Y) axis will be analysed (they will always have to correspond to values of the Marker studied), the ones for the abscissas “X” axis that will correspond to the gestational age in days or to the biometry related to the Gaussian Marker as well as the division factor by which the values of the abscissas (X) axis will be divided for their graphic and tabular presentation (normally 7 for the biochemical markers, which turns the days into weeks and 5 or 10 for the biometries expressed in millimeters like the CRL). Here again we can modify the intervals by direct input of the digits on the keyboard, or by the sliders, and their use in the case of the limits of the ordinates (Y) axis lies in the fact that it allows you to exclude extreme values from the markers which are often caused by errors in the input of screening data (the default minimum and maximum values are the same as the minimum and maximum values existing in the database). The values of the lower and upper limits of the abscissas (X) axis as well as the division Factor which are presented by default correspond with those which were defined for the marker in Equations Administration (Characteristics of the graph) but they can be modified making sure that the values set for both limits are an exact multiple of the division factor. Moreover, the difference between the higher and the lower limits divided by the division factor constitutes the number of “Cuts” or intervals into which the abscissas (X) axis will be divided.

The central part of the left panel displays, under the section “Equation”, a set of combos which allow choosing the type of equation (function) that will represent the regression of the values of the medians for each chosen marker in relation to gestational age calculated in days or in millimeters of its biometry. Currently, only polynomial function type up to fourth degree are accepted (5 coefficients, except in the log “e” and log10 transformations, which only allow 4 because of mathematical precision) with the different types of transformations allowed which can be applied to the
whole function or just or to the variable “X”. We must always ensure that the number of “Cuts” (week intervals or mm groups in biometries in which the marker is studied) greater than the number of the selected equation coefficients (function) as otherwise we obtain curves that cannot be used outside the extremes calculated and here big errors will occur.

Moreover, we can choose the equation existing in the database of the markers with which the new equation that is going to be calculated will be compared. This old equation, for comparison, will be presented in grey in the graphics. When one equation is selected a new button appears in the right panel, next to the graphic representation folder. This button when clicked displays a pop-up window with detailed information about this equation and the correspondent graphical representation.

Below the previous controls, we can find the “Specific Filters”; First, those for Start Date, and End Date, within which all the screenings for these dates recorded in the database (which meet the remaining conditions) will be included and can be handled directly from the keyboard with the help of a calendar or by means of the [+ ] and [- ] buttons which, respectively, increase or decrease one year in the displayed date.

The combo box “Centre” allows us to select the centre, provided that there is more than one present in the list, and the check box “Validation” only allows us to include the screenings with a validated result when it is checked.

The next filter is used to exclude the Markers of twin gestations from the set of screenings that will be used for the calculations, which is highly advisable and it is presented by default, as these gestations usually present results which are approximately double the normal ones for the gestational age and could alter the medians which are always calculated for single gestations. This is a check box which, when checked, excludes multiple pregnancies.

The next filter deals with the patients’ weight ranges within which all the patients whose weight is within both ranges will be included. These ranges can be modified by manual input of the digits, on the keyboard, or by means of the sliders.

The next set of filters called “Correction Factors Filter” displays a check box for each one of the correction factors defined in the Profile selected. When we check a correction factor’s check box, two combo boxes are displayed, to its right, that allow deciding if the screenings that present the above mentioned Correction factor (“Yes”), the ones that do not present it (“No”) or the ones in which it has not been assessed (“Not Assessed”) must be included in or excluded from the set of screenings that will be used for the calculations. Thus, for example, when the correction factor’s check box is checked, the intermediate drop-down list with “Exclude” and the drop-down list on the right with “Yes”, this means that all the screenings which have the said correction factor will be excluded, whereas all the others, that is, with the correction factor in “No” or “Not Assessed” will be included.
The “Generate PDF”, “Export Image” and “Export List” buttons, as all other tools, perform the functions that their names suggest.

On the left side of the upper sub-panel we will find the coefficients of the selected equation (function) from the analysed marker, and calculated for the screening records which have been included after applying the desired filters, and immediately below appear the coefficient of determination ($r^2$). The closer this coefficient gets to “1”, the higher the correlation between the real values of the medians obtained by mathematical calculation and the values obtained by applying the regression function estimated by this application. At the bottom, just below the previous one, appears the total number of samples (screenings) analysed and the “Cuts”, or subdivisions, made on the abscissas ($x$) axis. When it is not possible to make calculations of the medians due to errors in the choice of the selection filters, or to an insufficient number of samples, a warning text, in red, will appear informing about the type of error.

The chart on the right side of the upper panel displays in column form, starting from the left, the different intervals studied of gestation Weeks and days or biometry millimeters, the median of this biometry or of the gestation days (all that depending on whether it is a “days” biochemical marker or an “mm” ultrasound marker), the values of the real medians obtained by mathematical calculation for each interval, of the values in days or millimeters studied, and the ones obtained by applying the regression function estimated for this application.

The lower sub-panel on the right side of the screen displays a graphical representation of the regression function and its adaptation to the values of the different medians of the Marker for gestational age in days or millimeters so that the different Cuts analysed (intervals of the “X”-axis) can be observed, and if we position the cursor on the different medians obtained for each interval it shows the value of the corresponding abscissa and ordinate. Clicking the tab “Table” (the alternative to “Graphic representation”) displays a chart with the values of the median obtained by the regression function for each one point of the abscissas($x$)-axis.

As a general rule, to obtain a good regression function that represents as faithfully as possible the real medians of the Marker for each gestational age, we must use the best equation (with its transformation and number of coefficients) that produces a regression function (line) with the coefficient of determination $r^2$ the nearest to “1” possible, a graphic representation that adapts well to the real values of the medians, even in the extreme ones, that has a great similarity with the real biological curves published for the Marker and that, in no case, for any of the gestational ages, and especially in its limits in which the marker will be used, will produce negative results (less than “0”).
Calculation of the correction coefficients by maternal weight

Biochemical markers are substances that are produced by the fetus or the placenta and pass into the maternal circulation. Their concentration in the maternal blood is in inverse proportion to the volume in which they are diluted and this depends, mainly, on the maternal weight. For this reason, a correction specific to each biochemical marker will be necessary.

The purpose of this module is the completely automatic calculation of the maternal weight correction coefficients from the data obtained from the previously-tested patients.

At the moment two main acknowledged methods exist for maternal weight correction of biochemical markers: Neveux’s linear-reciprocal model and the linear-exponential power of 10 model. This module allows the calculation of the coefficients for both methods; the user can select which one is used for each biochemical marker. To obtain the correction coefficients for the maternal weight it is advisable to have a minimum of 1000 patients, otherwise the Program will inform the user that it is not advisable to use these because of low reliability.

This is a fairly complex screen divided into two panels: the left one and the right one which, in turn, is divided into upper sub-panel and lower sub-panel.

In the left panel, from top to bottom, we first find the button “Execute Query” which is used to run the process of this option once all the conditions (filters) have been entered, although in most cases we will not need to press it as it will be run automatically as soon as we have finished entering the conditions.

Below the “Make Query” button, we find the first controls grouped under the heading “Calculation”, which are used to select the Marker, for which we are going to calculate the correction coefficients for the Maternal Weight, which is part of a screening Profile, which we must select previously.

We can also choose the existing equation in the database of the corrections for maternal weight with which the new equation to be
calculated will be compared. This old equation, for comparison, will be presented in grey in the graphics. When one equation is selected a new button appears in the right panel, next to the graphic representation folder. This button when clicked displays a pop-up window with detailed information about this equation and the correspondent graphical representation.

Below the previous controls, we can find the “Specific Filters”;
First, those for Start Date, and End Date, within which all the screenings for these dates recorded in the database (which meet the remaining conditions) will be included and can be handled directly from the keyboard with the help of a calendar or by means of the [+} and [-] buttons which, respectively, increase or decrease one year in the displayed date.

The combo box “Centre” allows us to select the centre, provided that there is more than one present in the list, and the check box “Validation” only allows us to include the screenings with a validated result when it is checked.

The next filter is used to exclude the Markers of twin gestations from the set of screenings that will be used for the calculations, which is highly advisable and it is presented by default, as these gestations usually present results which are approximately double the normal ones for the gestational age and could alter the Correction Coefficients for the Maternal Weight which are always calculated for single gestations. This is a check box which, when checked, excludes multiple pregnancies.

The next set of filters called “Correction Factors Filter” displays a check box for each one of the correction factors defined in the Profile selected. When we check a correction factor’s check box, two combo boxes are displayed, to its right, that allow deciding if the screenings that present the above mentioned Correction factor (“Yes”), the ones that do not present it (“No”) or the ones in which it has not been assessed (“Not Assessed”) must be included in or excluded from the set of screenings that will be used for the calculations. Thus, for example, when the correction factor’s check box is checked, the intermediate drop-down list with “Exclude” and the drop-down list on the right with “Yes”, this means that all the
screenings which have the said correction factor will be excluded, whereas all the others, that is, with the correction factor in "No" or "Not Assessed" will be included.

At the bottom we find the "Divisor Factor(x)" that allows us to group the whole weight range (which will be selected with the following controls) in groups of Weight intervals (5 or 10 is normally taken in order to have the weights grouped in intervals of 5 or in intervals of 10), the above mentioned lower and higher limits of Maternal Weight within which all those between the two weight ranges will be included, which can be modified by direct input of the digits, on the keyboard or using the sliders.

The last control is a combo box that allows us to choose the type of Transformation that will be applied to the regression function that will correct the correct the Marker selected for the Maternal Weight and which, as mentioned before, can be chosen between the two acknowledged methods for the correction of the biochemical markers for the pregnant woman's weight: Neveux's linear-reciprocal (1/x) and the linear-exponential (10^x).

The "Generate PDF", "Export Image" and "Export List" buttons, as all other tools, perform the functions that their names suggest.

On the left side of the upper sub-panel we can view, from top to bottom, the type of Function calculated, the coefficients of that function of first-degree with its slope and intersection, and a series of Global data such as the number of samples (screenings) analysed, the median of the MoM if the correction is not applied, the median of the MoM that would be obtained after applying the calculated correction and the median of the Weight of the patients included in the calculation. When it is not possible to make calculations of the medians due to errors in the choice of the selection filters, or to an insufficient number of samples, a warning text, in red, will appear informing about the type of error.

The table on the right side of the upper sub-panel displays in columns, starting from the left, the different weight intervals analysed as well as, for each one of them, the number of screenings included, the Weight median, the median of the MoM uncorrected and the median of the MoM obtained by applying the correction.

The lower sub-panel on the right side of the screen displays the graphic with all the information obtained from the calculations and specifically the Black line shows the regression function calculated for the correction of the Maternal Weight, the Red line reshow the median of the MoM obtained if we apply the correction for the Maternal Weight and the Green line represents the median of the MoM obtained by applying the correction mentioned. Clicking the "Table" tab (the opposite from "Graphic Representation") displays a chart with the Weight Medians and the value obtained for each one of them when applying the regression function.

As a general rule, to obtain a good regression function that corrects in the best possible way the medians of the Marker for Maternal Weight, it is advisable to have more than 1000 screenings for the calculations, the global Median of the MoM.
should be as close to 1 as possible, and in any case it should be
closer than the one calculated without correction, and the Green
graphic, in the most frequent weight intervals in the screened
patients, should be closer to 1 MoM than the Red graphic.

**Calculation of predefined correction factors**

Specialized literature publishes correction factors or covariables
for race, twin pregnancies, smoking, insulin-dependent diabetes,
gestational bleeding, gravidity, assisted reproduction, fetal gender,
etc. However, each population’s ethnic and social characteristics
exercise a great influence on the importance that these factors can
have in the habitual screening practice. The reality is that studies
carried out in different screening services do not always provide
coinciding results when evaluating how and how much each
biochemical marker should be corrected in the presence of a
certain factor.

The function of this module is to allow each screening service to
calculate their own correction factors from previous experience
with a sample of pregnant women who present a specific factor, in
comparison to those who do not present the user-definable
correction factors, or covariables, definable by the user.

Mathematically, in this version of the Program, a correction factor
is a number by which the uncorrected Multiples of the Median
(MoM) are divided, thus obtaining MoM corrected by the correction
factor. In the event of the presence of different correction factors,
the MoM is divided by the successive correction factors.

This is a less complex screen than the previous ones divided into
two panels.

In the left panel, from top to bottom, we first find the button
“Execute Query” which is used to run the process of this option
once all the conditions (filters) have been entered, although in
most cases we will not need to press it as it will be run
automatically as soon as we have finished entering the conditions.

Below the previous panel, three combo boxes are displayed under
the heading “Correction Factor”. Here we must choose the
Predefined Correction Factor that we wish to calculate and the corresponding specific Marker that the corrective factor will modify which, in turn, is part of a screening Profile which we must previously select.

We can select the following filters: Start Date, and End Date, between which all the screenings for these dates recorded in the database (which meet the remaining conditions) will be included and can be handled directly from the keyboard with the help of a calendar or by means of the [+] and [-] buttons which, respectively, increase or decrease one year in the displayed date; the combo box “Centre” allows us to select the centre, provided that there is more than one present in the list; and the check box “Validation” only allows us to include the screenings with a Validated result to be included when it is checked; the filter that is used to exclude the Markers of twin gestations from the set of screenings that will be used for the calculations, which is highly advisable and it is presented by default, as these gestations usually present results which are approximately double the normal ones for the gestational age and could alter the Correction Factors which are always calculated for single gestations (this is a check box which, when checked, excludes multiple pregnancies) and the Filter that you to select the patients’ weight ranges within which all the patients whose weight is between both ranges will be included. These ranges can be modified by manual input of the digits, on the keyboard, or by means of the sliders.

On the right panel we can see the calculations performed and, from top to bottom, we find the number of samples, with and without the correction factor, analysed; the median of the MoM with and without the same correction factor; the Calculated Correction Factor (the summary itself), which, as already commented, divides the MoM by the said factor, as well as the value of the “z” statistic (of the normal distribution) and its significance level calculated with the Mann-Whitney or Wilcoxon two-tailed test (the level of statistical significance will depend, as well as the differences observed, on the size of the samples compared).

Immediately below we find a summary of the selection Filters that have been applied. When it is not possible to make calculations of the Marker’s Correction Factors due to errors in the choice of the selection filters, or to an insufficient number of samples, a warning text, in red, will appear informing about the type of error.

The “Generate PDF”, “Export Image” and “Export List” buttons, as all other tools, perform the functions that their names suggest.

As a general rule, in order to obtain a good Correction Factor that can best correct the Marker’s medians by the said factor, it is advisable to have at least 50 samples (screenings) which have the Predefined Corrected Factor, and a higher number which don’t, the difference between the calculated MoM, with and without the correction factor, must be statistically significant and the median of the MoM calculated with the Factor should be as close to “1” as possible.
Calculation of population distribution parameters
(Population variables)

The population variables are made up by the parameters which define the Gauss curve representing the marker values distribution for an affected and an unaffected population for a certain aneuploidy (mean and standard deviation) as well as the correlation coefficients that exist among the different marker combinations, used in a screening type, for fetuses affected and unaffected by the same aneuploidy.

The prenatal aneuploidy screening good practice guidelines advise that screening services must calculate their own population parameters for unaffected cases (it is rare that a screening service has enough casuistry for estimating them for affected fetuses), with the dual purpose of quality control and improvement of the screening results. This is the objective of this submenu which has, in turn, the following submenus: Gauss Curve, and Correlation Coefficients.

Calculation of population parameters. Gauss Curve

The Gauss curve, or the normal distribution of a marker for fetuses affected and unaffected by a given aneuploidy (trisomy 21 or trisomy 18), can be calculated by means of this option, presenting it graphically and defining it by means of the mean and standard deviation of the MoM. The values are previously log-converted to make the distribution as Gaussian as possible.

This is a fairly complex screen divided into two panels: the left one and the right one which, in turn, is divided into upper and lower subpanel.

In the left panel, from top to bottom, we first find the button “Execute Query” which is used to run the process of this option once all the conditions (filters) have been entered, although in most cases we will not need to press it, as it will be run automatically as soon as we have finished entering the conditions.

Below “Execute Query” we find the first set of controls, under the heading “Calculation”, which are used to select the Marker, for which we are going to calculate the mean and the standard deviation of the MoM (log10), which is part of a Screening Profile, which we must select previously, as well as the MoM type to be used in the calculations (MoM corrected by the different correction factors: weight, diabetes, race, etc., or Uncorrected, that is with no correction applied to them. We advise using the Uncorrected MoM, but excluding those screenings that present positive Correction Factors, multiple gestation or extreme-weight pregnancies, by applying the corresponding filters. The Minimum and Maximum boxes in the MoM exclude those values which are, respectively, below or above them as they are usually the consequence of errors in data inputting.

Below the previous controls, we can find the Filters mentioned above for the selection of the records to be included in the calculations; First, those for Start Date, and End Date, between which all the screenings for these dates recorded in the database
The combo box “Centre” us to select which centre, provided that there is more than one present in the list, and the “Validation” check box, when it is selected, allows us to include only the screenings with a validated result.

The next filter is used to exclude the Markers of twin gestations from the set of screenings that will be used for the calculations, which is highly advisable and it is presented by default, as these gestations usually present results which are approximately double the normal ones for the gestational age and could alter the MoM which are calculated, initially, for single gestations. This is a check box which, when ticked, excludes multiple pregnancies.

The next set of filters called “Correction Factors Filter” has a check box for each one of the correction factors defined in the Profile selected. When we check a correction factor’s check box, two combo boxes are displayed to its right, that allow deciding if the screenings that present the above mentioned Correction factor (“Yes”), the ones that do not present it (“No”) or the ones in which it has not been assessed (“Not Assessed”) must be included in or excluded from the set of screenings that will be used for the calculations. Thus, for example, when the correction factor’s check box is checked, the intermediate drop-down list with “Exclude” and the drop-down list on the right with “Yes”, this means that all the screenings which have the said correction factor will be excluded, whereas all the others, this is, with the correction factor in “No” or “Not Assessed” will be included.

The “Generate PDF”, “Export Image” and “Export List” buttons, as all other tools, perform the functions that their names suggest.

On the left side of the upper sub-panel we will find, from top to bottom, the results obtained with the mean and standard deviation log10 of the MoM and the number of samples, or screenings, analysed. On the right side of the upper sub-panel we will find a summary of the selection Filters applied.
Running the Program

The lower sub-panel on the right side of the screen displays the graphic of all the information obtained from the calculations made. Clicking the “Table” tab (the opposite from “Graphic Representation”) displays a chart with the number of cases for each represented interval and its values (we must remember that they are decimal logarithms.

**Calculation of population parameters. Correlation coefficients**

Knowledge of the correlation between each one of the possible marker pairs used in each Screening Profile is of vital importance so that the program understands the interdependence level among them, and is part of the so-called population parameters. The smaller the correlation between the different pairs of markers, the more effective combining them will be.

This option allows the calculation of Pearson’s Correlation Coefficient “r” between pairs of Gaussian markers, from the respective MoM log transformation, which makes the distribution as Gaussian as possible.

This is a fairly complex screen divided into two panels: left and right.

In the left panel, from top to bottom, we first find the button “Execute Query” which is used to run the process of this option once all the conditions (filters) have been entered, although in most cases we will not need to press it, as it will be run automatically as soon as we have finished entering the conditions.

Below the previous button we find the first set of controls, under the heading “Calculation”, which are used to select both markers, for which we are going to calculate Pearson’s Correlation Coefficient of the MoM (log10), which is part of a Screening Profile, which we must select previously, as well as the MoM type to be used in the calculations (MoM corrected by the different correction factors: weight, diabetes, race, etc., or Uncorrected, that is with no correction applied to them). We advise using the Uncorrected MoM, but excluding those screenings that present positive Correction Factors, multiple gestation or extreme-weight pregnancies, by applying the corresponding filters. The Minimum and Maximum boxes in the MoM of each Marker exclude those values which are, respectively, below or above them as they are usually the consequence of errors in data inputting.

Below the previous controls, we can find the Filters mentioned above for the selection of the records to be included in the calculations: First, those for Start Date, and End Date, between which all the screenings for these dates recorded in the database (which meet the remaining conditions) will be included and can be handled directly from the keyboard with the help of a calendar or by means of the [+–] buttons which, respectively, increase or decrease one year in the displayed date.

The combo box “Centre” allows us to select the centre, provided that there is more than one present in the list, and the “Validation” check box, when it is selected, allows us to include only the screenings with a validated result.
The next filter is used to exclude the Markers in twin gestations from the set of screenings that will be used for the calculations, which is highly advisable and it is presented by default, as these gestations usually present results which are approximately double the normal ones for the gestational age and could alter the MoM which are calculated, initially, for single gestations. This is a checkbox which, when checked, excludes multiple pregnancies.

The next set of filters called “Correction Factors Filter” displays a checkbox for each one of the correction factors defined in the Profile selected. When we tick a correction factor’s checkbox, two combo boxes are displayed to its right, that allow deciding if the screenings that present the above mentioned Correction factor (“Yes”), the ones that do not present it (“No”) or the ones in which it has not been assessed (“Not Assessed”) must be included in or excluded from the set of screenings that will be used for the calculations. Thus, for example, when the correction factor’s checkbox is checked, the intermediate drop-down list with “Exclude” and the drop-down list on the right with “Yes”, this means that all the screenings which have the said correction factor will be excluded, whereas all the others, this is, with the correction factor in “No” or “Not Assessed” will be included.

The “Generate PDF”, “Export Image” and “Export List” buttons, as all other tools, perform the functions that their names suggest.

Below the previous panel we can see the result obtained, this is, Pearson’s Correlation Coefficients, whose values may vary between “0” (absence of correlation) and “1” (total correlation as the one presented when analysing the correlation of a marker with itself). Below the result, a summary of the selection filters applied to the calculations is displayed.

**Statistics**

This submenu has 5 new submenus for the computation and presentation of the following statistical parameters: Maternal age distribution, Distribution of maternal weight, Distribution of gestational age, Distribution of correction factors, and Median MoM by markers.
Maternal age distribution

This screen displays the distribution of maternal age at screening of selected patients who have been chosen by means of adequate filters, in graphic and tabular format, as well as the mathematical parameters that define that distribution.

The screen is divided into two panels: the left one and right one which in turn is divided into upper sub-panel and lower sub-panel.

In the left panel, from top to bottom, we first find the button “Execute Query”, which is used to run the process of this option once all the conditions (filters) have been entered, although in most cases we will not need to click it, as it will be run automatically as soon as we have finished entering the conditions.

Immediately below, we find the “Filters” that allow the selection of the screenings that will be included in the query and whose statistical data will be presented. We can select from two Dates, by Centre, for validated screenings, and by one specific screening Profile or all of them.

Checking the “Debug” check box displays the composition of the query in XML format.

In the upper right sub-panel we find the button that allows you to print the results and the graph in PDF format, and, below this button, the numerical statistical results which include: the mean and standard deviation in total number of samples (differentiating between those assessed and those whose assessment has not been possible), the sample’s maximum and minimum ages, as well as the number and percentage of those over 30, 35 and 40 years old. The right side of this sub-panel shows a summary of the filters applied.

The lower right sub-panel displays the results in graphic or tabular format (depending on which tab we select). We can select the ordinates (Y) axis values to be displayed in number or percentage, and for the abscissas (X) axis we can select the age range that will appear in the graph.
Distribution of maternal weight

This screen shows the distribution of maternal weight at screening of selected patients who have been chosen by means of adequate filters, in graphic and tabular format, as well as the mathematical parameters that define that distribution.

The screen is divided into two panels: the left one and the right one which in turn is divided into upper sub-panel and lower sub-panel.

In the left panel, from top to bottom, we first find the button “Execute Query”, which is used to run the process of this option once all the conditions (filters) have been entered, although in most cases we will not need to press it, as it will be run automatically as soon as we have finished entering the conditions.

Immediately below, we find the “Filters” that allow the selection of the screenings that will be included in the query and whose statistical data will be presented. We can select from two Dates, by Centre, for validated screenings, and by one specific screening Profile or all of them.

At the top of the upper right sub-panel we find the button to print the results and the graph in PDF format, and, below this button, the numerical statistical results which include: the mean and standard deviation, minimum and maximum weights of the sample, the percentiles 25, 75 and 50 (median), the number and percentages of weights below 30 kilos and above 120, the total number of samples and the number and percentage of those whose evaluation has not been possible. The right side of this sub-panel shows a summary of the filters applied.

The lower right sub-panel displays the results in graphic or tabular format (depending on which tab we select). We can select the ordinates (Y) axis values to be presented in number or percentage.

Distribution of gestational age

This screen shows the distribution of gestational ages at screening of selected patients who have been chosen by means of adequate...
filters, in graphic and tabular format, as well as the mathematical parameters that define that distribution.

The screen is divided into two panels: the left one and the right one which in turn is divided into upper sub-panel and lower sub-panel.

In the left panel, from top to bottom, we first find the button “Execute Query”, which is used to run the process of this option once all the conditions (filters) have been entered, although in most cases we will not need to press it, as it will be run automatically as soon as we have finished entering the conditions.

Immediately below, we find the “Filters” that allow the selection of the screenings that will be included in the query and whose statistical data will be presented. We can select from two Dates, by Centre, for validated screenings, and by one specific screening Profile or all of them. We can also select the abscissas (x) axis to show the gestational age in Days or in weeks.

At the top of the upper right sub-panel we find the button that allows you to print the results and the graph in PDF format, and, below this button, the numerical statistical results which include: the mean and standard deviation, minimum and maximum gestational age of the sample, the percentiles 25, 75 and 50 (median), the number and percentages of gestational ages below 70 day and above 108 and 140, the total number of samples and the number and percentage of those whose evaluation has not been possible. The right side of this sub-panel shows a summary of the filters applied.

The lower right sub-panel displays the results in graphic or tabular format (depending on which tab we select). We can select the ordinates (Y) axis values to be displayed in number or percentage, and for the abscissas (X) axis we can select, by means of a sliding control, the age range that will appear in the graph.

**Distribution of correction factors**

This screen shows the distribution of the Predefined, or user-definable, Correction Factors at the time of the screening of the
selected patients, who have been chosen using the adequate filters, in graphic and tabular format, as well as the mathematical parameters that define the distribution.

The screen is divided into two panels: the left one and the right one which in turn is divided into upper sub-panel and lower sub-panel.

In the left panel, from top to bottom, we first find the button “Execute Query”, which is used to run the process of this option once all the conditions (filters) have been entered, although in most cases we will not need to press it, as it will be run automatically as soon as we have finished entering the conditions.

Immediately below, we find the “Filters” that allow the selection of the screenings that will be included in the query and whose statistical data will be shown. We can select between two Dates, by Centre, for validated screenings, by one specific screening Profile or all of them, and especially the type of Correction Factor that is going to be evaluated.

At the top of the upper right sub-panel we find the button that allows you to print the results and the graph in PDF format and, below this button, the numerical statistical results which include: the total number of samples analysed and the number and percentage of screenings whose Correction Factor is Present (Yes), Absent (No) or Not Assessed. The right side of this sub-panel shows a summary of the filters applied.

The lower right sub-panel displays the results in graphic or tabular format (depending on which tab we select). We can select the ordinates (Y) axis values to be shown in number or percentage.

**Markers mean MoM**

This screen displays the distribution of the MoM of the markers of a specific Profile and of the selected patients, who have been chosen using the adequate filters, in graphic and tabular format, as well as the mathematical parameters that define the distribution.
The screen is divided into two panels: the left one and the right one which, in turn, is divided into upper sub-panel and lower sub-panel.

In the left panel, from top to bottom, we first find the button “Execute Query”, which is used to run the process of this option once all the conditions (filters) have been entered, although in most cases we will not need to press it, as it will be run automatically as soon as we have finished entering the conditions.

Immediately below, we find the “Filters” that allow the selection of the screenings that will be included in the query and whose statistical data will be presented. We can select from two Dates, by Centre, whether the screenings have been Validated or not, and by a specific Screening Profile. We can also choose the MoM type analysed (corrected by the different Correction Factors or Not corrected by any Factor), as well as the interval of the MoM that will be used in the calculations to exclude limit MoMs which are often the consequence of errors when inputting data in the Program.

At the top of the upper right sub-panel we find the button that allows you to print the results and the graph in PDF format and, below this button, the numerical statistical results which include: the mean and the conventional standard deviation and the log10 for each analyzed Marker as well as the number of samples (in table format). The right side of this sub-panel shows a summary of the filters applied.

The lower right sub-panel displays the results in graphic or tabular format (as selected with the tabs on the two folders present). We can select the values of the Y axis to be presented in decimal format or in log10.

**Validation**

This submenu presents two options: Biochemistry Validation and Risk Validation.
Biochemistry Validation

For the laboratories with a high volume of screening samples the validation of the biochemical results one by one of the Screening Search, Blood test Search or Patients Administration screens, takes too much of their time. The purpose of this screen is to facilitate the validation of the screenings’ biochemical analysis in a very fast but also efficient way, as it allows you to view the selected biochemical analysis between two dates, as well as by Centre and screening Profile, which are not validated with their most important details like: Identification, Name and Surname, Maternal Age, Gestational Age, sample Date, sample Code, screening Profile and Multiples of the Median (MoM) of the biochemical markers of the Profile (if all the listed records are from the same Profile, that is, the same markers, the heading of the columns of the MoM has the name of the markers, whereas if there are records from different Profiles, the heading of the columns of the MoM shows the marker’s order number within each Profile, and when we place the cursor on each of the MoM of the different records, a tooltip text is displayed specifying the name of the marker, as well as its real value, that of the MoM corrected and uncorrected and the calculated Risks for the trisomies and for preeclampsia as in the other cases).

The gestational age, the MoM and the Risks are provisionally calculated from the Last Menstrual Period (LMP) when its calculation is not possible with a biometry (usually the cephalo-caudal length: CRL) because an ultrasound for dating the gestation has not been performed yet, whereas when the program has the ultrasound biometry it estimates the gestational age from it, which is more accurate.

At the top of the right table or grid we find 3 buttons that allow respectively, from right to left: “Deselect all”, which unchecks the check box with the same name, situated right next to the test tubes icon before each record; “Select all”, which checks all the check boxes and “Validate selected” for the global validation of all the records selected with a check mark. It is also possible to select or unselect each record individually by placing the cursor on each check box.
By clicking the button with the test tubes icon of a specific record the complete screening record is displayed, viewed through the screening administration folders, which is very useful when we want to view all its details, even though it is slow. In most cases the screenings can be perfectly validated with the sufficient information in the screen and it saves a significant amount of time.

**Risk Validation**

This submenu, very similar to the previous one in layout and function, allows the Validation, case-by-case or en bloc, of the calculated Risks in the “Risk” folder from the “Screening” window and tab.

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**“Administration” menu**

It is the third menu in the top Menu bar and includes a series of functionalities for Advanced Administration of Users, Persons, Sonographers, Constants, Equations, Profiles, Biometrics and the Multiple Languages, Temporary Events and Administration Reports.

Access to the various submenus depends on the privilege of each individual user, most of which are exclusively reserved for the Administrators.

As many of the options in the Administration menus include controls which may have Multi-language Codes (those controls that show in its right end an icon with an oblique label), in the first part of this section we will explain the basic operation of these controls and how to define a Multi-language Code and the corresponding translations into the languages provided by the Program.

**Multi-language Code Selector/Editor**

This pop-up screen, common to all the controls that use Multi-language Codes for screen presentation of the texts in the language set by the client, is activated and displayed when clicking the button with the label icon to the right of the control with the Multi-language code. This way it is possible to establish different texts for each language for the same control or label that appears in the client’s screen.

The toolbar at the top of this screen has a text box called “Multi-language Code” which has or allows you to enter the “searching” code and a drop-down list, at the right end, which allows us to select only one language, or all (empty). The toolbar immediately below shows the number of pages that the “search” code displays, and the whole lower panel displays the mentioned codes with their respective translations.

Below this panel there is another toolbar with the “Select Multi-language code” “Duplicate”, “Add” and “Delete”, with the functions that their names suggest. By clicking on the “Select Multi-language
In the text boxes (lines) located immediately below “Translations” we must enter the translations into the different preestablished languages which are displayed with the flag icon corresponding to the language of the respective country located at the right end of each text box, with their translation. In this right end, just above the flags, we find the “Select multi-language code” and “Edit” buttons.

How to make a New Multi-language Code and its Translations

All the names which have a button on the right with a label icon (such as Profile Name, Marker Name, Equation Name, etc.) are Multi-language names and to be modified and translated into the different languages we must use the screen which is displayed when clicking that button, called “Multi-language Code Selector/Editor” or by means of the “Multi-language Administration” menu, but this can only be done by an Administrator with all the necessary permissions.

In order to enter a New Multi-language Code and its corresponding texts in the numerous languages that the Program admits we must proceed as follows:

We enter the name of a multi-language code present in the text box above (the one with the funnel icon) if we wish to use it as the basis for duplicating it (by clicking the “Duplicate” button) and then modifying it (either the code or the translations), or creating a new one by entering its code (which must begin with ID_) in the text box with the “Select Multi-language code” at the right end (just below the tool bar) that is displayed by clicking the “Add” button. In both cases we must click the “Save” or “Cancel” buttons that
appear over the translations once we’ve entered them (either new or modified) in their respective text boxes with the flag icons.

For the multi-language code it is advisable to use the names that suggest their content.

In order to transfer the multi-language code and the respective translations to the text or label for which they have been established we must click the “Select Multi-language code” or the icon located at the right end of the multi-language text box and the pop-up window for Multi-language Administration will close. During this process the Program may inform that the System has automatically Updated or that it is necessary to click the Update System button at the bottom of the screen in order to include the modifications for the calculation engine.

**Persons, Users, Doctors... Administration**

This submenu intended to select, through other submenus, and supply User code, Password and the access permissions to all the possible Program users. It has the following submenus: Persons Administration, Users Administration, Sonographers Administration, Doctors in Invasive Techniques Administrations, Requesting Doctors Administration and Signatory Doctors Administration.

**Persons Administration**

![Persons Administration Screen]

This is a screen designed to register the affiliation of all the professionals who will take part in the Program regardless of their access levels or privileges and whether they are active or not. It has no other function than managing the professionals' database and it does not allow assigning passwords or other permissions to them.

It has two different panels, left and right. The left one displays in grid or table format the list of all the individuals recorded in the
database with their Name, Surname and NIC (sorted by NIC) and when we select an individual from this list all his/her data appear in the right panel (Selected Person) and can be edited.

The right panel has the following edit buttons at the top: “Add” (“+” icon), which allows you to add a new subject, “Edit” (paper and pencil icon), which allows you to modify the data, “Delete” (“-” icon) which deletes permanently the selected person, “Save” (floppy disk icon) which saves the changes made and “Cancel” (“x” icon) which revokes the changes made unless they have been saved. In the upper right corner, next to the close box of this screen ([x]), there is an icon with two green horizontal arrows in opposite directions which allows you to update the server database so that the modifications have an immediate effect in the whole computer system.

Below the toolbar we find the following identification data: NIC, Name, Surname, Address and Postal Code, City and Country of residence, Telephone 1 and 2, e-mail and a text box for a description of other information such as role in the screening program, etc.

It is highly advisable for all the Program Users to be registered in this database to enter them as Users in the specific module “Users Administration” to be able to assign permissions and passwords.

**How to enter a New Person**

Only an Administrator with the necessary permissions can register the affiliation of all the professionals who will take part in the Program regardless of their access levels or privileges and whether they are active or not. To do so, the Administrator must use the Administration submenu called “Persons Administration”.

To enter a New “Person” we must press the “Add” button which will display all the empty boxes where we can enter all their data, which must have at least: Name, Surname, and NIC.

Once all the changes have been made, we must Save them and press “Update System” (the button next to the close box in the upper right corner of this screen with an icon with two green horizontal arrows in opposite directions) and so the New Person will be registered in the database and available for all the options which users and all client computers can view.

**Users Administration**

This screen is intended to provide the user Code, the Password and access permissions to all the possible users of the Program. Although new users can be entered here, it is highly advisable to previously register them in the “persons Administration” screen, as this way all their data will be available in case we have to contact them, for example.

It has two different panels, left and right. The left one displays in grid or table format the list of all the individuals registered as Users with their NIC and User Code (sorted by User Code) and when we
select an individual from this list all his/her data appear in the right panel (Selected User) and can be edited.

The right panel has the following edit buttons at the top: “Add” (“+” icon), which allows you to add a new subject, “Edit” (paper and pencil icon), which allows you to modify the data, “Delete” (“-” icon) which deletes permanently the selected person, “Save” (floppy disk icon) which saves the changes made, “Cancel” (“x” icon) which revokes the changes made unless they have been saved and “Reset Password” which allows you to remove the Password assigned to the selected User (as it cannot be viewed if it has been forgotten) and assigning a provisional new one which is highly advisable to change in its first use. In the upper right corner, next to the close box of this screen ({$x$}), there is an icon with two green horizontal arrows in opposite directions which allows you to update the server database so that the modifications have an immediate effect in the whole computer system.

Below the toolbar we can find, from left to right, “User Data” with the User Code (the one that will be used to access the Program together with the Password), a check box which confirms if the user is Active and, if it is the case of entering a new user, they will be assigned a provisional password (which, as mentioned, is highly advisable to change in the first use of the Program).

In the section “Associated centres” the user must check the respective check boxes that appear before each item in the list to state if he/she is associated to one or more of the Centres available in the list (the elements in this list are configured and defined in the “Constants Administration” screen, specifically in the “Centres” section.

On the right side of the right panel, the “Related Person” combo is displayed. It allows us to select and view which Person (from the “Persons Administration” table) is the User displayed in this panel. To its right we find two buttons with the magnifying glass and the spanner.

Clicking the button with the magnifying glass displays the “Selected Person Viewer” which allows us to view and edit the person’s filiation data while clicking the button with the spanner, displays the “Persons Administration” screen, which is described specifically, and which enables the display of all recorded Persons and their individual selection and edition.
The “User Profile” combo allows you to select the type of basic User Profile, and here we understand the concept of User Profile as a type of activity with which a set of Roles or specific permissions are associated. Thus, an “ADMIN_TOTAL” user will have most of the roles (which are displayed in the list just below this combo with a check box before each one to verify if the user has the necessary permissions to run this Role), while a “SONOGRAPHER” user will only have the typical roles for his/her task. By being assigned a User profile, a user acquires a series of predefined roles but the Administrator can increase or decrease them by checking or unchecking the corresponding check boxes from the “Associated Roles” list just below the combos.

The list of roles, whose denomination is written in upper-case letters, also has, next to each role, their descriptions (what their functionalities in the program are) in English.

How to enter a New User

Only an Administrator with the necessary permissions can enter a New “User”. To do so, we must press the “Add” button which will display all the empty boxes where we can enter the User Code (the one that will be used to access the Program, together with the Password); the Provisional Password (which, as already mentioned, is very convenient to change in the first access to the
Program), whether the User is Active or not, by means of the corresponding check box; the Associated Centres (whether the User is associated to one or more of the Centres available in the list whose elements are configured and defined in the “Constants Administration” screen, specifically in the “Centres” (screening centres) section; the combo for the “Related person”, which allows us to select and view which Person (from the “Persons Administration” table) who is the User shown in this panel and has, to its right, two buttons with the magnifying glass and the spanner by means of which he/she can be entered as a new user in case this has not been done previously through “Persons Administration”; The “User Profile” combo, which allows you to select the type of basic User Profile, and here we understand the concept of User Profile as a type of activity with which a set of Roles or specific permissions are associated, which can be modified, removed or added by checking or unchecking the corresponding check boxes from the “Associated Roles” list which is situated below on the right.

Once all the changes have been made, we must Save them and press “Update System” (the button next to the close box in the upper right corner of this screen with an icon with two green horizontal arrows in opposite directions) and so the New Person will be recorded in the database and available for all the options which users and all client computers can view.

**How to Reset the Password**

Each user’s password is secret and nobody knows it, not even the Program Administrators. So, if a User forgets his/her Password, nobody can remind it to him/her, and in this case the only option is to Reset that Password (erase it) and assign them a provisional new one which the user should modify the next time that the Program is used.

Only a System Administrator can Reset the Password provided that he/she has all the necessary permissions, but in each installation at least one must be able to do it.

It is just a matter of selecting User for whom this operation must be carried out (from the left column in the “Users Administration” screen) and clicking the Reset Password button. The program will request the New Password, we enter it and Accept. Remember that passwords are case sensitive.

**Sonographers Administration**

The administration of Ultrasound Units and Sonographers is a fairly complex task in an aneuploidy screening program as in general, there are different ultrasound units performing ultrasounds for the same Centre, or for different Centres, and in some units there may be multiple sonographers who, in turn, may carry out their activity in different ultrasound units simultaneously. And to make things even more complicated it has been suggested, as a measure to reduce variability in the measurements of ultrasound markers, that each sonographer should use his/her
own medians equation for the calculation of the MoM of the Gaussian ultrasound markers (Nuchal Translucency, etc.).

This screen allows the coordination of all these multiple relations between Centres, Ultrasound Units, Sonographers and specific or general Sonographer Equations.

The relationship between Centre (the highest or broadest level that can, on its own or associated with other Centres, organize and carry out an aneuploidy screening program and in practice corresponds with a Hospital or Health Centre which has at least one laboratory and professional obstetricians able to request and inform the patient about the result of the screening) and the Ultrasound Centres (Ultrasound Units) is established and explained in the “Constants Administration” section, specifically in the “Ultrasound Centres” table.

This screen displays four different panels, two on the left, each one in list form, and two on the right for the edition of the selected member from the left list, and of its same level.

The list with the names of the “Available Ultrasound Units” is displayed in the top left panel and the selected one can be edited in the corresponding top right panel (its Identification Code and Descriptive Name) and it can be associated with a Centre from the lower list which matches with the ones in the “Centre” table in the “Constants Administration” list by checking the corresponding check box to its left. At the top we can find the edit buttons: “Edit” (paper and pencil icon), which allows you to modify the data, “Delete” (“-“ icon) which deletes permanently the selected person, “Save” (floppy disk icon) which saves the changes made, “Cancel” (“x” icon) which revokes the changes made unless they have been saved and “Update System” which allows you to update the server database so that the modifications have an immediate effect in the whole computer system.
In the lower left panel we can find the list of the Sonographers corresponding to the Ultrasound Unit selected from the upper left list, with surname, name and NIC (sorted by NIC) and the selected one can be edited, or new ones can be added, in the lower right panel which has two buttons at the top: “Add” (“+” icon), which allows you to add a new sonographer, “Edit” (paper and pencil icon), which allows you to modify the data, “Delete” (“-“icon) which deletes permanently the selected sonographer, “Save” (floppy disk icon) which saves the changes made and “Cancel” (“x” icon) which revokes the changes made unless they have been saved.

Below the buttons we can find the “Person” drop-down list which allows us to select and view which Person (from the “Persons Administration” table) is the Sonographer presented in this panel and to its right we find two buttons with the magnifying glass and spanner icons.

By clicking the magnifying glass icon we find the “Selected Person Viewer” which allows us to show and edit its filiation data, while by clicking the spanner button we find the “Persons Administration” screen, which is described specifically and allows the visualization of the recorded Persons and the selection and edition of one of them.

When we wish to associate a Specific Equation with the selected sonographer we must check the Ultrasound Marker to which we have to associate the Specific Equation from the list of equations presented (with the equation’s identifying numeric code and its name) at the bottom of the screen, we must also tick the check box on its right and at this moment a combo appears where we can view or enter the specific equation for this marker and sonographer with the button with the magnifying glass icon, which is used, in this case, to open the pop-up window for the “Selected Equation Viewer” which, as its name suggests, allows you to view and editing the equation listed in the combo.

**How to enter a New Sonographer**

Providing you are an Administrator and have the necessary permissions, the Sonographers Administration will allow you to enter new Sonographers and, if necessary, to assign a specific equation to each one of them for the Gaussian Ultrasound Markers (medians of the marker for specific biometries).

The first thing to do is to select in the upper left panel, from the list with the names of the “Ultrasound Units Available”, the one that the new sonographer will belong to. It can be edited in the corresponding upper right panel (its identification Code and descriptive Name), and it can also be associated to a Centre from the list below which corresponds with the ones in the “Centre” table in the “Constants Administration” screen by checking the respective check box to its left.

In the lower left panel we find the list of the Sonographers corresponding to the Ultrasound Unit selected in the upper left list and a new one can be added with the Add button in the lower right panel.
Below the buttons we can find the “Person” drop-down list which allows us to select and view which Person (from the “Persons Administration” table) is the Sonographer presented in this panel and to its right we find two buttons with the magnifying glass and spanner icons.

By clicking the magnifying glass icon we find the “Selected Person Viewer” which allows us to view and edit his/her filiation data, while by clicking the spanner button we find the “Persons Administration” screen, which is described specifically and allows the visualization of the recorded Persons and the selection and edition of one of them.

When we wish to associate a Specific Equation with the selected sonographer we must check the Ultrasound Marker to which we have to associate the Specific Equation from the list of equations presented (with the equation’s identifying numeric code and its name) at the bottom of the screen, we must also tick the check box on its right and at this moment a combo appears where we can view or enter the specific equation for this marker and sonographer with the button with the magnifying glass icon, which is used, in this case, to open the pop-up window for the “Selected Equation Viewer” which, as its name suggests, allows you to view and editing the equation listed in the combo.

Finally, clicking the “Update System” button allows you to update the server database so that the modifications made have an immediate effect in the whole computer system.

**Doctors in Invasive Techniques Administration**

This is a fairly simple screen for the administration and identification of all those professionals who will be responsible for carrying out the Invasive Techniques and who, in many cases, will not have another role in the Screening Program. Their names will appear in the drop-down list “Doctor Responsible for Invasive Technique” in the folder with the same name.

It has two different panels, left and right. The left one displays in grid or table format the list of all the individuals recorded in the database with the “IT Unit Id” to which they are assigned and NIC (sorted by NIC) and when we select an individual from this list he/she will appear with this same data in the right panel and can be edited.

The right panel has the following edit buttons at the top: “Add” (“+” icon), which allows you to add a new subject, “Edit” (paper and pencil icon), which allows you to modify the data, “Delete” (“-” icon) which deletes permanently the selected person, “Save” (floppy
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disk icon) which saves the changes made and “Cancel” (“x” icon) which revokes the changes made unless they have been saved. In the upper right corner, next to the close box of this screen ([x]), there is an icon with two green horizontal arrows in opposite directions which allows you to update the server database so that the modifications have an immediate effect in the whole computer system.

Below the toolbar we find the following identification data: Invasive Techniques Unit Identification (IT Unit Id*) and a large combo, with the “NIC*” label where the adequate person (with NIC, Surname and Name) is presented or selected. To its right we find two buttons with the magnifying glass and spanner icons.

By clicking the magnifying glass icon we find the “Selected Person Viewer” which allows you to view and edit his/her filiation data, while by clicking the spanner button we find the “Persons Administration” screen, which is described specifically and allows the visualization of the recorded Persons and the selection and edition of one of them.

**Requesting Doctors Administration**

This is a fairly simple screen for the administration and identification of all those professionals who will be responsible for requesting screenings and who, in many cases, will not have another role in the Screening Program. Their names will appear in the drop-down list “Screening Applicant” in the screening folder with the same name, assuming that the option of their record is contemplated in Settings.

It has two different panels, left and right. The left one displays in grid or table format the list of all the individuals recorded in the database with the “Centre” to which they are assigned and NIC (sorted by NIC) and when we select an individual from this list he/she will appear with this same data in the right panel and can be edited.

The right panel has the following edit buttons at the top: “Add” (“+” icon), which allows you to add a new subject, “Edit” (paper and pencil icon), which allows you to modify the data, “Delete” (“-” icon) which deletes permanently the selected person, “Save” (floppy disk icon) which saves the changes made and “Cancel” (“x” icon) which revokes the changes made unless they have been saved. In the upper right corner, next to the close box of this screen ([x]), there is an icon with two green horizontal arrows in opposite directions which allows you to update the server database so that the modifications have an immediate effect in the whole computer system.
Below the toolbar we find the following identification Data: Centre which he/she is associated to (Centre *) and a large combo, with the “NIC” label where the adequate person (with NIC, Surname and Name) is presented or selected. To its right we find two buttons with the magnifying glass and spanner icons.

By clicking the magnifying glass icon we find the “Selected Person Viewer” which allows you to view and edit his/her filiation data, while by clicking the spanner button we find the “Persons Administration” screen, which is described specifically and allows the visualization of all the recorded Persons and the selection and edition of one of them.

**Centres, Laboratories … Administration**

This submenu is used for the administration of the various Centres, Units, Laboratories, i.e. all the functional units involved in the screening process and perinatal outcome. It has the following submenus: Centre Administration, Biochemical Laboratories Administration, Sampling Modules Administration, Ultrasound Units Administration, Invasive Techniques Laboratories Administration, Invasive Techniques Units Administration, Morphological Ultrasound Units Administration and Birth Centres Administration.

**Centre Administration**

This screen allows the administration and identification of those Centres which will organize a screening program around them, which means that it is the highest rank of the organization whose task is to offer the prenatal screening to the patients. In general, it will be a high-level Hospital which will have one or more
laboratories and one or more ultrasound unit. As in a population screening program, for example at provincial or autonomous community level, there may be several hospitals or associated “Centres” associated which cooperate in it, there may also be more than one Centre and it is on this screen where they are identified and entered. Their names will appear identified in many different screens and the criteria “Centre” will allow all the professionals who belong to it, (provided they have the appropriate permission) to consult all the patients from that Centre, whereas, in general, they will not be able to consult the data of the patients from other Associated centres, except for the filiation in the Patients Data folder.

It has two different panels, left and right. The left one display, in grid or table format, the list of all the Centres recorded in the database with Identification number, Name of the Centre and Description and allows you to select a centre, which will be displayed on the right panel with the same data and can be edited.

The right panel has the following edit buttons at the top: “Add” (“+” icon), which allows you to add a new subject, “Edit” (paper and pencil icon), which allows you to modify the data, “Delete” (“-” icon) which deletes permanently the selected person, “Save” (floppy disk icon) which saves the changes made and “Cancel” (“x” icon) which revokes the changes made unless they have been saved. In the upper right corner, next to the close box of this screen ([x]), there is an icon with two green horizontal arrows in opposite directions which allows you to update the server database so that the modifications have an immediate effect in the whole computer system.

Below the toolbar we find the following identification Data: Identification number (id*), Name of the Centre and its description which may be very complete.

**Biochemical Laboratories Administration**

This is a screen which allows us to administrate and identify those Clinical Analysis Laboratories that take part in the population screening program determining the Biochemical Markers and relating them with its hierarchical “Centre”.

There are three differentiated panels, one on the left, one in the centre and one on the right. The left one displays in grid or table format the list of all the Laboratories recorded in the database with the Identification number and the Name as it appears in the Multi-language code, and allows you to select a laboratory, which will be displayed in the central panel and can be edited.
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The central panel has the following edit buttons at the top: “Add” (“+” icon), which allows you to add a new subject, “Edit” (paper and pencil icon), which allows you to modify the data, “Delete” (“-” icon) which deletes permanently the selected person, “Save” (floppy disk icon) which saves the changes made and “Cancel” (“x” icon) which revokes the changes made unless they have been saved. In the upper right corner, next to the close box of this screen ([x]), there is an icon with two green horizontal arrows in opposite directions which allows you to update the server database so that the modifications have an immediate effect in the whole computer system. Below the toolbar we can see the following identifying Data: the Identification number (Biochemical Lab id*) and below that, we find the Name in Multi-language code, which can be edited and modified by clicking the button with the oblique label icon to the right of the text box.

The panel on the right is to relate each Biochemical Laboratory with one or more screening Centres and to do so we check the corresponding check box situated before each defined Centre and press the upper button with a floppy disk icon to save that relationship in the database.

**Sampling Modules Administration**

Many clinical laboratories have various sampling modules, or small satellite laboratories to make access easier for the clients, and it is important for the population screening program to have evidence of the Sampling Module where the first stages in the determination of the biochemical markers were carried out. This screen allows you to relate, administrate and identify those Sampling Modules which depend on a specific Clinical Analysis Laboratory.

It has two different panels, left and right. The left one displays in grid or table format, the list of all the Biochemical Laboratories recorded in the database with their Identification number, the Identification Number of each Sampling Module related to it and the Multi-language Code of the name given to the Sampling Module, and allows you to select one of them, which will be displayed on the right panel with the same data and can be edited.
The right panel has the following edit buttons at the top: “Add” (“+" icon), which allows you to add a new subject, “Edit” (paper and pencil icon), which allows you to modify the data, “Delete” (“-" icon) which deletes permanently the selected person, “Save” (floppy disk icon) which saves the changes made and “Cancel” (“x" icon) which revokes the changes made unless they have been saved. In the upper right corner, next to the close box of this screen ([x]), there is an icon with two green horizontal arrows in opposite directions which allows you to update the server database so that the modifications have an immediate effect in the whole computer system.

Below the toolbar we can see the following identifying Data: the Identification number of the Biochemical Laboratory (Biochemical Lab id*), the Identification number of the Sampling Module (Sampling Module id*) and its Name in Multi-language code, which can be edited and modified by clicking the button with the oblique label icon to the right of the text box.

**Ultrasound Units Administration**

This is a screen which allows you to administrate and identify those Ultrasound Units that take part in the population screening program determining the Ultrasound Markers and relating them with their hierarchical “Centre”.

There are three differentiated panels, one on the left, one in the centre and one on the right. The left one displays in grid or table format the list of all the Ultrasound Units recorded in the database with the Identification number and the Name as it appears in the Multi-language code, and allows you to select one of them, which will be displayed in the central panel and can be edited.

The central panel has the following edit buttons at the top: “Add” (“+” icon), which allows you to add a new subject, “Edit” (paper and pencil icon), which allows you to modify the data, “Delete” (“-” icon) which deletes permanently the selected person, “Save” (floppy disk icon) which saves the changes made and “Cancel” (“x"
icon) which revokes the changes made unless they have been saved. In the upper right corner, next to the close box of this screen ([x]), there is an icon with two green horizontal arrows in opposite directions which allows you to update the server database so that the modifications have an immediate effect in the whole computer system. Below the toolbar we can see the following identifying Data: the Identification number (id*) and below that, we find the name of the Ultrasound Unit.

The panel on the right is to relate each Ultrasound Unit with one or more screening Centres and to do so we check the corresponding check box situated before each defined Centre and press the upper button with a floppy disk icon to save that relationship in the database.

**Invasive Techniques Laboratories Administration**

The samples obtained by means of an invasive technique can be processed by different laboratories depending on the type of material and the technique requested (karyotype in amniotic fluid, karyotype in the chorion, QF PCR, etc.). A list of these laboratories will appear in the Invasive Techniques folder so that we can select the right one for each of the requested determinations. This screen allows you to manage and identify Invasive Techniques Laboratories.

It has two different panels, left and right. The left one display, in grid or table format, the list of all the Invasive Techniques Laboratories recorded in the database with their Identification number and the Name of the Invasive Techniques Laboratory and allows you to select each one, which will be displayed on the right panel with the same data and can be edited.

The right panel has the following edit buttons at the top: “Add” (“+” icon), which allows you to add a new subject, “Edit” (paper and pencil icon), which allows you to modify the data, “Delete” (“-” icon) which deletes permanently the selected person, “Save” (floppy disk icon) which saves the changes made and “Cancel” (“x” icon) which revokes the changes made unless they have been saved. In the upper right corner, next to the close box of this screen ([x]), there is an icon with two green horizontal arrows in opposite directions which allows you to update the server database so that the modifications have an immediate effect in the whole computer system.

Below the toolbar we can see the following identifying Data: the Identification number of the Invasive Techniques Laboratory (Invasive Technique Lab id*) and its name.
Invasive Techniques Units Administration

This screen allows you to manage and identify Invasive Techniques Units, which is the place where the patients’ samples will be drawn.

It has two different panels, left and right. The left one displays, in grid or table format, the list of all the Invasive Techniques Units recorded in the database with their Identification number and the Name of the Invasive Techniques Unit and allows you to select each one, which will be displayed on the right panel with the same data and can be edited.

The right panel has the following edit buttons at the top: “Add” (“+” icon), which allows you to add a new subject, “Edit” (paper and pencil icon), which allows you to modify the data, “Delete” (“-” icon) which deletes permanently the selected person, “Save” (floppy disk icon) which saves the changes made and “Cancel” (“x” icon) which revokes the changes made unless they have been saved. In the upper right corner, next to the close box of this screen ([x]), there is an icon with two green horizontal arrows in opposite directions which allows you to update the server database so that the modifications have an immediate effect in the whole computer system.

Below the toolbar we can see the following identifying Data: the Identification number (id*) and the name given to the Invasive Techniques Unit.

Morphological Ultrasound Units Administration

This screen allows you to manage and identify the Ultrasound Morphological Units, which is the place where the explorations will be performed on the patients (they will not always be the same as the Units where the Ultrasound Markers or Biometries are assessed, which are managed in the Ultrasound Unit Administration in this same section). A list of them appears in the respective combo in the Morphological Ultrasounds folder.

It has two different panels, left and right. The left one displays, in grid or table format, the list of all the Morphological Ultrasound
Units recorded in the database with their Identification number and the Name of each Morphological Ultrasound Unit and allows you to select each one, which will be displayed on the right panel with the same data and can be edited.

The right panel displays, at the top, the edit buttons: “Add” (“+” icon), which allows you to add a new subject, “Edit” (paper and pencil icon), which allows you to modify the data, “Delete” (“-” icon) which deletes permanently the selected person, “Save” (floppy disk icon) which saves the changes made and “Cancel” (“x” icon) which revokes the changes made unless they have been saved. In the upper right corner, next to the close box of this screen ([x]), there is an icon with two green horizontal arrows in opposite directions which allows you to update the server database so that the modifications have an immediate effect in the whole computer system.

Below the toolbar we can see the following identifying Data: the Identification number (id*) and the name given to the Morphological Ultrasound Unit.

**Birth Centres Administration**

This screen allows you to manage and identify the centres or hospitals where the patients give birth.

It has two different panels, left and right. The left one displays, in grid or table format, the list of all the Birth Centres recorded in the database with their Identification number and the Name given to each Birth Centre and allows you to select each one, which will be displayed on the right panel with the same data and can be edited.

The right panel has, at the top, the edit buttons: “Add” (“+” icon), which allows you to add a new subject, “Edit” (paper and pencil icon), which allows you to modify the data, “Delete” (“-” icon) which deletes permanently the selected person, “Save” (floppy disk icon) which saves the changes made and “Cancel” (“x” icon) which revokes the changes made unless they have been saved. In the upper right corner, next to the close box of this screen ([x]), there is an icon with two green horizontal arrows in opposite directions which allows you to update the server database so that the modifications have an immediate effect in the whole computer system.

Below the toolbar we can see the following identifying Data: the Identification number (id*) and the Name given to the Specific Birth Centre.
Dynamic Lists Administration

This submenu is used for the administration of the various lists that appear in the combos, that is, the Program’s combo boxes, which can be configured by the Program Administrator/s. It has the following submenus: Race Administration, Ethnos Administration, Countries Administration, Abortion types Administration, Birth types Administration, Types of Congenital Anomalies and Invasive Techniques Results Administration, Types of Indications in Invasive Techniques Administration, Administration of types of processing on Invasive Techniques and Morphological Ultrasound Results Administration.

Race Administration

This screen allows you to manage and identify the possible Races of the patients, which are a correction factor and are displayed in the drop-down list in the patient's filiation data, and as a check box (when in fact it is a correction factor) in the screening folder.

It has two different panels, left and right. The left one displays, in grid or table format, the list of all the Races defined with their Identification Code, Multi-language Code, Default Description and Value, and allows you to select each one, which will be displayed on the right panel with the same data and can be edited.

The right panel has the following edit buttons at the top: “Add” (“+” icon), which allows you to add a new subject, “Edit” (paper and pencil icon), which allows you to modify the data, “Delete” (“-“ icon) which deletes permanently the selected person, “Save” (floppy disk icon) which saves the changes made and “Cancel” (“x” icon) which revokes the changes made unless they have been saved. In the upper right corner, next to the close box of this screen ([x]), there is an icon with two green horizontal arrows in opposite directions which allows you to update the server database so that the modifications have an immediate effect in the whole computer system.

Below the toolbar we can see the following identifying Data: the Code (Code*), the name of the Multi-language Code, the Description also in Multi-language Code (these two have a button, to the right of the text box, with the oblique label icon which allows you to assign the Multi-language Code and its translations into the different predefined languages) and a check box that assigns which one of the different races is the value that will appear by default on the screen when we open it.
Countries Administration

This screen allows you to manage and identify the different Countries that will appear in the different drop-down lists, which allow selecting, for example, the patient’s birth country or residence.

It has two different panels, left and right. The left one displays in grid or table format, the list of all the Countries defined with their Identification Code and Multi-language Code, and allows you to select each one, which will be displayed on the right panel with the same data and can be edited.

The right panel has the following edit buttons at the top: “Add” (“+” icon), which allows you to add a new subject, “Edit” (paper and pencil icon), which allows you to modify the data, “Delete” (“-” icon) which deletes permanently the selected person, “Save” (floppy disk icon) which saves the changes made and “Cancel” (“x” icon) which revokes the changes made unless they have been saved. In the upper right corner, next to the close box of this screen ([x]), there is an icon with two green horizontal arrows in opposite directions which allows you to update the server database so that the modifications have an immediate effect in the whole computer system.

Below the toolbar we can see the following identifying Data: the Identification Code (Code*) and the name of the Multi-language Code for each Country, which has, to the right of the text box, a button with the oblique label icon which allows you to assign the Multi-language Code and its translations into the different predefined languages.

Abortion types Administration

This screen allows you to manage and identify the different abortion types (it refers to when a pregnancy ends in a spontaneous or induced abortion) that will appear in the drop-down list in the Perinatal Outcome folder.

It has two different panels, left and right. The left one displays in grid or table format, the list of the different abortion types defined with their Identification Code and Multi-language Code, and allows
you to select each one, which will be displayed on the right panel with the same data and can be edited.

The right panel has the following edit buttons at the top: “Add” (“+” icon), which allows you to add a new subject, “Edit” (paper and pencil icon), which allows you to modify the data, “Delete” (“-” icon) which deletes permanently the selected person, “Save” (floppy disk icon) which saves the changes made and “Cancel” (“x” icon) which revokes the changes made unless they have been saved. In the upper right corner, next to the close box of this screen ([x]), there is an icon with two green horizontal arrows in opposite directions which allows you to update the server database so that the modifications have an immediate effect in the whole computer system.

Below the toolbar we can see the following identifying Data: the Identification Code (Code*) and the name of the Multi-language Code for each type of Abortion, which has, to the right of the text box, a button with the oblique label icon which allows you to assign the Multi-language Code and its translations into the different predefined languages.

**Screening suspension causes Administration**

Screen with design and function similar to the previously mentioned one but intended for the classification of the reasons why the screening may have been suspended before it was completed.

**Birth types Administration**

This screen allows you to manage and identify the different birth types (it refers to when a pregnancy ends in childbirth with a fetus alive or not, healthy or not, etc.) that will appear in the drop-down list in the Perinatal Outcome folder.

![Birth Type Administration](image)

It has two different panels, left and right. The left one displays in grid or table format, the list of the different birth types defined with their Identification Code and Multi-language Code, and allows you to select each one, which will be displayed on the right panel with the same data and can be edited.

The right panel has the following edit buttons at the top: “Add” (“+” icon), which allows you to add a new subject, “Edit” (paper and pencil icon), which allows you to modify the data, “Delete” (“-” icon) which deletes permanently the selected person, “Save” (floppy disk icon) which saves the changes made and “Cancel” (“x” icon) which revokes the changes made unless they have been saved. In the upper right corner, next to the close box of this screen ([x]), there is an icon with two green horizontal arrows in opposite
directions which allows you to update the server database so that the modifications have an immediate effect in the whole computer system.

Below the toolbar we can see the following identifying Data: the Identification Code (Code*) and the name of the Multi-language Code for each type of Birth, which has, to the right of the text box, a button with the oblique label icon which allows you to assign the Multi-language Code and its translations into the different predefined languages.

**Types of Congenital Anomalies and Invasive Techniques Results Administration**

This screen allows you to manage and identify the different Types of Congenital Anomalies defined and coded (it refers to the list of Congenital Anomalies that can affect the fetus) that will appear in different drop-down lists in the Invasive Techniques, Morphological Ultrasound and Perinatal Outcome folders. As not all the pathologies listed here must appear in each one of the drop-down lists, this screen also allows you to define in which list or lists each one of them will appear.

It has two different panels, left and right. The left one displays in grid or table format, the list of the different Types of Congenital Anomalies defined with their Identification Code, Multi-language Code, and whether they have to be used in the Invasive Techniques, Morphological Ultrasound and/or Perinatal Outcome screens and allows you to select each one, which will be displayed on the right panel with the same data and can be edited.

The right panel has the following edit buttons at the top: “Add” (“+” icon), which allows you to add a new subject, “Edit” (paper and pencil icon), which allows you to modify the data, “Delete” (“-” icon) which deletes permanently the selected person, “Save” (floppy disk icon) which saves the changes made and “Cancel” (“x” icon) which revokes the changes made unless they have been saved. In the upper right corner, next to the close box of this screen ([x]), there is an icon with two green horizontal arrows in opposite directions which allows you to update the server database so that the modifications have an immediate effect in the whole computer system.

Below the toolbar we can see the following identifying Data: the Identification Code (Code*), the name of the Multi-language Code for each Type of Congenital Anomaly, which has, to the right of the text box, a button with the oblique label icon which allows you to assign the Multi-language Code and its translations into the different predefined languages, and 3 check boxes to define if the
selected one must be included, or not, in the list that appears in the Invasive Techniques, Morphological Ultrasound or Perinatal Outcome screens.

**Types of Indications in Invasive Techniques Administration**

This screen allows you to manage and identify the different types of Indications in Invasive Techniques (it refers to the reason why an Invasive Technique is indicated) that will appear in the drop-down list in the Invasive Techniques folder.

It has two different panels, left and right. The left one displays in grid or table format, the list of the different Types of Indications in Invasive Techniques defined with their Identification Code, and the Multi-language Code, and allows you to select each one, which will be displayed on the right panel with the same data and can be edited.

The right panel has the following edit buttons at the top: “Add” (“+” icon), which allows you to add a new subject, “Edit” (paper and pencil icon), which allows you to modify the data, “Delete” (“-” icon) which deletes permanently the selected person, “Save” (floppy disk icon) which saves the changes made and “Cancel” (“x” icon) which revokes the changes made unless they have been saved. In the upper right corner, next to the close box of this screen ([x]), there is an icon with two green horizontal arrows in opposite directions which allows you to update the server database so that the modifications have an immediate effect in the whole computer system.

Below the toolbar we can see the following identifying Data: the Identification Code (Code*), and the name of the Multi-language Code for each Type of Indications in the Invasive Techniques, which has, to the right of the text box, a button with the oblique label icon which allows you to assign the Multi-language Code and its translations into the different predefined languages.

**Types of Procedures in Invasive Techniques Administration**

This screen allows you to manage and identify the different Types of Procedures in Invasive Techniques (it refers to the approach method and material obtained in an invasive technique such as amniocentesis or transabdominal or transcervical chorionic villus sampling, etc.) that will appear in the drop-down list in the Invasive Techniques folder.
It has two different panels, left and right. The left one has, in grid or table format, the list of the different Types of Procedures in Invasive Techniques defined with their Identification Code, and the Multi-language Code, and allows you to select each one, which will be displayed on the right panel with the same data and can be edited.

The right panel has the following edit buttons at the top: “Add” (“+” icon), which allows you to add a new subject, “Edit” (paper and pencil icon), which allows you to modify the data, “Delete” (“-” icon) which deletes permanently the selected person, “Save” (floppy disk icon) which saves the changes made and “Cancel” (“x” icon) which revokes the changes made unless they have been saved. In the upper right corner, next to the close box of this screen ([x]), there is an icon with two green horizontal arrows in opposite directions which allows you to update the server database so that the modifications have an immediate effect in the whole computer system.

Below the toolbar we can see the following identifying Data: the Identification Code (Code*), and the name of the Multi-language Code for each Type of Procedure in the Invasive Techniques, which has, to the right of the text box, a button with the oblique label icon which allows you to assign the Multi-language Code and its translations into the different predefined languages.

Types of Studies on Invasive Techniques Administration

This screen allows you to manage and identify the different Types of Studies performed on the material obtained by means of the Invasive Techniques (karyotype in different tissues, QF PCR, FISH, etc.) that will appear as Types of Test, with check box, centre where it is processed, identification type, outcome and date, in the Invasive Techniques folder.

It has two different panels, left and right. The left one displays in grid or table format, the list of all the different Types of Blood test in Invasive Techniques defined with their Identification Code, and the Multi-language Code, and allows you to select each one, which will be displayed on the right panel with the same data and can be edited.
The right panel has the following edit buttons at the top: “Add” (“+” icon), which allows you to add a new subject, “Edit” (paper and pencil icon), which allows you to modify the data, “Delete” (“-” icon) which deletes permanently the selected person, “Save” (floppy disk icon) which saves the changes made and “Cancel” (“x” icon) which revokes the changes made unless they have been saved. In the upper right corner, next to the close box of this screen ([x]), there is an icon with two green horizontal arrows in opposite directions which allows you to update the server database so that the modifications have an immediate effect in the whole computer system.

Below the toolbar we can see the following identifying Data: the Identification Code (Code*), and the name of the Multi-language Code for each Type of Blood test in the Invasive Techniques, which has, to the right of the text box, a button with the oblique label icon which allows you to assign the Multi-language Code and its translations into the different predefined languages.

**Morphological Ultrasound Results Administration**

This screen allows you to manage and identify the different Types of Global Results in a Morphological Ultrasound (it refers to whether the Morphological Ultrasound has been satisfactory in establishing if the fetus is apparently normal, if a congenital anomaly has been confirmed, if a congenital anomaly has been suspected or it just has not been possible to come to a conclusion) that will appear in the drop-down list in the Perinatal Outcome folder.

It has two different panels, left and right. The left one displays in grid or table format, the list of all the different Types of Results in a Morphological Ultrasound defined with their Identification Code, and the Multi-language Code, and allows you to select each one, which will be displayed on the right panel with the same data and can be edited.
The right panel has the following edit buttons at the top: “Add” (“+” icon), which allows you to add a new subject, “Edit” (paper and pencil icon), which allows you to modify the data, “Delete” (“-” icon) which deletes permanently the selected person, “Save” (floppy disk icon) which saves the changes made and “Cancel” (“x” icon) which revokes the changes made unless they have been saved. In the upper right corner, next to the close box of this screen ([x]), there is an icon with two green horizontal arrows in opposite directions which allows you to update the server database so that the modifications have an immediate effect in the whole computer system.

Below the toolbar we can see the following identifying Data: the Identification Code (Code*), and the name of the Multi-language Code for each Type of Result in a Morphological Ultrasound, which has, to the right of the text box, a button with the oblique label icon which allows you to assign the Multi-language Code and its translations into the different predefined languages.

### Administration of Calculation Variables

This submenu is used for the administration of all the constants and variables used by the Program in Risk calculations. For this reason its influence on the outcome of the Screening is enormous and only those Administrators with sufficient training in the scientific bases of aneuploidy prenatal screening must manage, modify or add parameters. It has the following submenus:

- Screening Profiles
- Equations
- Gaussian Markers
- Dichotomous Markers
- Correction Factors
- Biometries
- Types of Screening
- Types of Screening Profile

#### Screening Profiles Administration

This is the main administration menu of the Program from the point of view of Risk and gestational age calculation. It is a relatively complex screen due to the great configurability of the Program and it is organized into eight folders (Screening Profiles, Equations, Gaussian Markers, Dichotomous Markers, Correction Factors, Biometries, Types of Screening and Types of Screening Profile) at the top of the screen. The first folder has, in turn, nine sub-folders with their editing buttons listed in a line below its name (Screening Profiles) and the type of Profile: Profile Variables, Global Configuration, GM, GM Correlation, DM, BMI, Biometries, Secondary Risks and Description.

The eight folders located at the top of the screen have the following functions:

- “Screening profiles”, with its nine sub-folders, allows you to define all the constants and variables used by the program for the risk calculations. It will be explained in detail further below.
- “Equations”: all the equations used for the calculations are defined here. It will also be explained in more detail further below.
- “Gaussian Markers” allows you to define the name and type of each one of the Gaussian markers, the units of measurement used
in the assessment, as well as the names they will be given in the different languages and in the reports.

“Dichotomous Markers” allows you to define the name and type of each one of the Dichotomous markers, previously called likelihood ratio (LR) markers, soft markers or true-false markers, as well as the names they will be given in the different languages and in the reports.

“Correction Factors” allows you to define the different correction factors or “covariables” that will intervene in the different markers, their association with other variables and the names they will be given in the different languages and in the reports.

“Biometries” allows you to define the name and type of each one of the different biometries used by the program for the calculation of the gestational age, or other intermediate variables (NT), as well as the names they will be given in the different languages and in the reports.

“Types of Screening” allows you to specify which type of Risks will be calculated separately as well as the names they will be given in the different languages, the calculation type (Gaussian or Simple), who is affected by the Risk (the mother or the fetus), etc. For example, one Type of Screening may be for trisomies 18-13 either together or separately for trisomy 18 and trisomy 13.

“Types of Screening Profile” allows you to define the Profile Types considered in a global way, basically considered from the point of view of the moment of the pregnancy in which they are performed, (aneuploidies during the first and second trimester of the gestation or integrated screenings or screenings for preeclampsia) as well as the names they will be given in the different languages.

**Toolbar controls.** At the top of the screen, and from left to right, we find the following controls: The combo for the identification and selection of the profile whose data will be displayed in all the controls of this screen, the “Duplicate” button, which, as its name suggests, takes the data from the current profile and creates a completely new one based on the existing one which can later be modified (to avoid creating a new one from the beginning), the “Edit” button to modify the selected profile, the “Delete” button to remove permanently the selected profile, the “Save” button to save the modifications made, the “Cancel” button which revokes the changes made unless they have been saved, “Block” which prevents from accidental or deliberate modifications in all the controls of this menu and screen (for the important consequences that they may have on the Risk calculations) and “Update System” to update the server’s database so that the modifications have an immediate effect in the whole computer system.

**Profile variables folder**

In this folder we can select, and see a summary of them, all the Types of Screening, Gaussian Markers, Correction Factors and Biometries that take part in the risk calculations of the selected Profile. By means of the drop-down list located at the top of each group we can choose and add elements by clicking the “+” button,
delete them by clicking the “-” button, to the right of each element, or change the order in which they are displayed (upwards or downwards) using the up/down arrows.

On the lower side of this folder we can see the “centres” affected by the Profile selected.

**Global Settings**

It is divided into two sub-panels, left and right. They are organized as follows, from top to bottom:

The left sub-panel (Generic Configuration) shows the code and number of the Screening Profile, with its different names in multi-language, the Type of Screening Profile with its state (Active or Discarded), the priority in the way it is arranged (in the combos), the upper and lower limits of the maternal age and gestational age with which the risk calculations will be made, the method used for the calculations in twins (SsdwLab5 of specific population variables, Wald 1991 or Wald 2003) and, finally, whether sonographers’ identification will be required.

The right sub-panel (specific calculation Configurations by screening) shows the cut-off points, in the Risk, for each one of the Types of screening with the maximum and minimum values which will appear in the printed report (the screen always displays the real Risks, whereas in the report they appear truncated by the mentioned cut-off points), the rates of increase in the Risk when there are antecedents of trisomy, NTD, etc. in a previous pregnancy, the calculation method used for Risk estimation for the patient’s age with a correction factor (divides the risk by the mentioned factor) for each Type of screening and finally the correction for late fetal loss (intrauterine lethality), that is, whether the risk will be expressed at time of delivery (at term) or at the time of the screening, and in this last case an upward correction will be applied, defined by the equation selected from the corresponding drop-down list.

**GM (Gaussian Markers) folder**

This folder contains one sub-folder for every Gaussian marker that has been defined. Each sub-folder has the title of the Gaussian marker used as well as the measurement units used for its assessment. The controls that allow entering the data will vary depending on the type of marker (Biochemical, Ultrasound, MAP (mean arterial pressure) or Doppler), but there will always be two sub-panels, left and right, explained as follows, from top to bottom:

The left sub-panel (General Data) shows the Equation of the medians (MoM) used for their assessment, the correction for the maternal weight and the equation used for that, a list with the correction factors that will affect it, as well as the value of the correction which can be entered as a unique value (by clicking the graph symbol, which will display the corresponding drop-down list for the equation selected). At the bottom, below the list of the correction factors, the correction factor for mono and dichorionic twins is displayed, also selectable as a unique value or as an equation (only for the Wald methods in twins).
The right sub-panel contains two sub-folders (configuration by Screening and Comments).

The “Configuration by Screening” sub-folder allows you to select, for each Type of Screening, whether the Marker has to be used in the Risk calculations and also whether it must be excluded in the calculations of Monochorionic or Dichorionic twins. It also allows you to enter, for each Type of Screening (type of trisomy or preeclampsia), the values of the Log10 Median for Affected and Unaffected fetuses (the ones for Affected fetuses can be selected as a unique value or equation, as in the previous sub-folder), the Standard Deviations and the truncated values, upper and lower in the MoM which limit the MoM that take part in the calculations when they reach extreme values. Finally, when the calculation method used for twin gestations is SsdwLab5 (with its own population parameters), combo boxes are displayed which allow entering the value of the mentioned population parameters (Log10 Median for affected an Unaffected fetuses) in the form of equations.

The “Comments” sub-folder can only be used for explanatory comments about the way the selected marker is used in the calculations. It has no influence on the risk calculations.

**GM (Gaussian Markers) Correlation folder**

In different panels, one for each Type of Screening, it displays the correlation factors, between pairs of markers Unaffected and Affected by the screened pathology (trisomy 21, 18-13, 18 or 13 independently, early preeclampsia (EPE) or late preeclampsia (LPE), etc.). It uses the markers’ short names in the different lines and columns with their multi-language text, and the correlation between each marker must always be “1”.

**DM (Dichotomous Markers) Folder**

This folder displays in different panels, one for each Type of Screening, the list of Dichotomous Markers (soft markers and/or LR markers) which have been defined for the Screening Profile in the “Profile Variables” folder, each one with a check box to the right of the name which is used to inform the program whether to use them for the corresponding Type of Screening (trisomy 21, 18-13, EPE, LPE, etc.) when the check box is selected, or not to use them if the box is not selected. There are also two text boxes with the heading LR- and LR+ where to enter the corresponding Negative and Positive Likelihood Ratio. A “1” value entered in both text boxes means that the marker will not take part in the calculations but it will be possible to assess it in the screening screens and, later, calculate its positive and negative LR, that is, it enables its use for investigation.

At the end of the identification number of the DM there is a 1T, 2T or PE text, which is tells whether it is, respectively, a first-trimester, second-trimester or preeclampsia marker. This can be especially useful when, for example, on a first-trimester combined screening we wish to make a recalculation of the Risk with dichotomous markers, in which case we will use the first-trimester (1T) markers if the ultrasound assessment of the DM is performed during the
first trimester. On the other hand, if we perform the ultrasound for the DM during the second trimester (with a combined screening for the first trimester as we mentioned above) we will use all the “2T” markers.

Immediately below the heading of each list of dichotomous markers, there is a check box with the text: “Use Dichotomous Markers LR” which enables the whole lot of DM for their use, or not, in the Risk Calculations for the Screening profile selected, and specifically for the Type of Screening Profile with the check box.

**BMI (Body Mass Index)**

In the screening for Preeclampsia the BMI is used as a criteria for the calculation of basal Risk (the equivalent to Risk for maternal age in aneuploidy screening) with specific *Likelihood Ratio (LR)* for the different Body Mass intervals, which may be different for the different types of preeclampsia (EPE or LPE).

This folder, which has one panel for each type of preeclampsia defined in the “Profile Variables” folder, allows you to enter the lower and upper limits in the BMI which subdivide the different intervals and the LR that will be applied in each one.

**Biometries**

This relatively simple folder allows you to enter, by means of drop-down menus, the different equations which represent the biometries that will be used for dating the pregnancy (gestational age calculation or GA) and, for each one, which criteria will be used in twin pregnancies (the highest, the lowest, the arithmetic mean or the geometric mean) as well as defining one of them as default for the GA calculations.

**Secondary Risks**

The “Secondary Risks” folder displays all the Risks that can be calculated, on the screen and/or in the reports, as well as the Main Risk (for example Risk for Trisomy 21 or for Early Preeclampsia), that is, intermediate Risks which are calculated before obtaining the Main Risk (risk for maternal age in the trisomies, basal risk of preeclampsia, etc.), or combinations of one or more markers that take part in Risk calculations such as the risk based exclusively on the biochemistry, the risk based exclusively on the ultrasound, the risk of a unique marker, etc. The check boxes allow us to decide which of these Secondary Risks will be shown on the screen and which is the limit beyond which they will considered as positive.

**Description**

The only function of this folder is to allow a detailed description of the parameters used in the Profile with its bibliographic origin, modifications made, etc., as well as the origin of the reagents used, medians, population parameters, etc. It is only descriptive and does not take part in the Risk calculations but it automatically registers the original Profile taken at the time of making new profiles.
How to Make a New Screening Profile

The SsdwLab6 software offers a great facility for the design of New Screening Profiles, which is not always an easy task in most software for aneuploidy screening, especially when they present a higher configurability.

So, the only way to create a New Screening Profile in all the SsdwLab series programs (as long as one is Administrator and has the necessary permissions) is duplicating a previous pre-existing Profile which is taken as the basis for the new one in all its parameters (clicking the “Duplicate” button in the top toolbar in the Profile Manager screen having the Profile that we want to take as the basis displayed on the screen and whose name appears in the idProfile combo). The duplicate Profile can, from here, be modified in all its parameters as long as it is not locked and it has not been used for any Risk calculation. When duplicating a Profile the software asks us to assign a new Identification Code for the New Profile which must be unique and new.

To add New (not defined previously) Gaussian Markers, Dichotomous Markers, Correction factors, Biometries, Types of Screening or even Types of Screening profile, we must open the corresponding folder (the one above the drop-down list that displays the code and name of the screening profiles available, and above the edit buttons) and complete all the specific parameters, most of them common to all of them, such as the Identification Number, the Code and the multi-language Name that will be displayed on the screen and the one for the printed report, the Short Name, and other parameters which are specific to each one of them, such as the evaluation Units, and the Type of Marker for the “Gaussian Markers”, which type of exploration it is associated with as in the “Dichotomous Markers”, the different Types of associations to covariables for the “Correction Factors”, the Calculation Type, Risk Type (maternal or fetal), and the way their Diagnosis will be assessed in the different “Types of Screening”, etc. The specific aspect of “Equations” will be dealt with, in more detail, in the following sections.

If we wish to add one of the following to a New Screening Profile: Gaussian Markers, Dichotomous Markers, Correction Factors, Biometries, Screening profiles or even Types of Screening profile, previously existing in their respective folders, we must add them in the corresponding column in the first folder of the Screening Profile (Profile Variables) by displaying them in the respective drop-down list and clicking the “+” icon (or delete it with the “-” icon) or we can change the display order by means of the up/down arrows. The calculation parameters for these new markers, correction factors, etc. must be entered in the respective folders in the Screening Profile (Global Configuration, GM, GM Correlation, DM, BMI and Biometries).

All the names which have the button with the label icon (as Profile Name, etc.) at their right end are Multi-language names and to modify and translate them into the different languages, we can either use the screen that is displayed when clicking the said
button called “Multi-language Code Selector/Editor” or the option menu “Multi-language Administration” as described in “How to make a New Multi-language Code and its Translations”.

Once all the modifications have been made we must Save the changes, Lock the Profile so it cannot be modified accidentally and finally click Update System and so the New Profile will be available to all the clients.

Equations Administration

This is a relatively complex screen which allows you to define each and every equation (formulae) that the program uses for Risk calculations. The equations may be polynomial, logistic, additive exponential or additive square root; they may have between one and six coefficients (when it has only one it is used as a constant) and several transformations may be applied to the same equation (reciprocal, exponential, power of 10, etc.) or to the independent variable “x”.

On the left side of the screen all the available equations are displayed, (they are numbered manually following these recommended steps: 1-299 generic equations; 200-399 equations for maternal weight correction; 400-999 equations of medians; 1000-1999 equations of Log10 Median MoM; 2000-2999 equations for twins in SsdwLab5 and 3000-3999 equations for the calculation of gestational age) at the time of their creation, and the whole of the right side is occupied by the different sections of the equation selected on the left.

On the top right side of the screen we find the equation’s edit buttons with the following functions: “Add” to enter a new equation, “Duplicate” allowing to build on the current equation to make a new one, “Edit” to modify the selected equation, “Delete” to remove it permanently, “Save” to save the modifications made, “Cancel” to revoke the changes made unless they have been saved and “Update System” to update the server’s database so that the modifications have an immediate effect in the whole computer system.

Below the buttons we find 3 sub-panels (the lower right one displays 4 folders) which display the characteristics of the equation selected and are described below from top to bottom:

The left panel displays the Identification number of the equation, its Name in the Multi-language Code and the name it gets in the language in which the client is configured. To the right of the Name it gets from the Multi-language Code there is a button with a label icon which we click to access the Multi-language Code Selector/Editor which is described at the end of this section. Below this identification data we find the Type of equation (polynomial, logistic, additive exponential or additive square root) and the transformation that can be applied to it (reciprocal, exponential or power of 10). Below this we find the “X” axis Limits, which may be configured as: Without limits, Do not calculate when it is outside range or Apply truncation when outside range (in these last two cases, text boxes are displayed that allow entering the lower and
upper limits). Immediately below we find the Configuration of the “X” variable, to which we can apply a transformation (reciprocal, exponential, power of 10, logarithmic to the base “e” or logarithmic to the base 10) or a correction Constant, in its respective text box, with a check box which, if checked, can be displayed in weeks. Next is the Configuration of the “Y” variable to which a corrective or multiplier constant may be applied by entering the values in the respective text boxes. Below this we find a frame which displays the mathematical Representation of the equation, and at the very bottom there are some mathematical applications which, by means of web links, display further details and editing possibilities of the equation.

The upper right panel shows the 6 possible coefficients of the equation selected called from C0 to C5 which represent respectively letters a, b, c, d, e, and f from the nomenclature of the equations ordered from top to bottom. When there is a unique coefficient, which will be C0, the equation represents a constant and there can be no empty spaces between the coefficients.

The lower right panel has 4 folders that display, respectively, the graphic representation of the equation, the definable parameters of its graphic Configuration, the table of Values and its description.

The Graphic Representation folder can only be modified through the configuration of the parameters of the second folder where the characteristics of the Abscissas (X) and the Ordinates (Y) can be defined: for each one, we can define their lower and upper Limits, the assessment units with their multi-language text, and for the Abscissas we can also define the distance between columns and the division factor, while for the Ordinates it is only possible to show a second line (by means of a check box) and in this case to indicate the value, in the “Y” axis, of this second line.

The Values folder displays, in table format, the values for the “X” and their corresponding values for the “Y”. Finally, the Description folder allows us to detail the origin, function, etc. of the mentioned equation, and, if it has been duplicated, it automatically displays the identifying code of the original equation.

How to formulate a New Equation

Unlike Profiles, Markers and Correction Factors, and providing you are an Administrator and have the necessary permissions, Equations Administrator (which is accessible from the submenu with the same name in the Administration menu, or from the Gaussian Markers Administration screen, etc.) allows you to formulate a new equation with all its properties starting from zero, by means of the Add or Duplicate buttons, as in the previous ones, taking an existing equation as the basis and then modifying its properties. In the first case, that is, by means of the Add button, a screen with only empty boxes is displayed, so they must be completed manually as explained in “Equations Administration”; whereas with the Duplicate button the equation displayed and all its characteristics are the same as the equation taken as the basis.
(the one selected from the list on the left of the screen), the only difference being the new Identification Code.

All the names which at their end have a button with the icon of a label (like the Name of the Equation, etc.) are multi-language names and for their modification and translation into the different languages we must use the screen that appears when clicking that button called “Multi-language Codes Selector/Editor”, or the "Multi-language Administration" menu option, as described in “How to make a New Multi-language Code and its Translations”.

Once all the modifications have been made, we must Save them and press Update System and so the New Equation will be available for a New Marker, if this task has been performed, and for all the clients.

Configuration

This submenu displays a unique menu: Multi-language Administration.

Multi-language Administration

This is a Multi-language Program and as such allows the user to establish and modify all those words which have, on the screen, a “label” icon on the button at the right end of the text box in which they are displayed. The Program also allows the user to establish or modify the respective translations into the languages configured in the Program.

This screen is an expansion or extension of the floating window of the “Multi-language Administrator”, mentioned above, which is displayed when clicking the button with the label icon which all the Multi-language codes have.

The screen is divided into two panels: one on the left and one on the right. The left panel displays a list of all existing multi-language codes. At the top of the panel there is a text box for entering a new code (by clicking the “+” icon) or for finding an existing one (just by
entering its code), and on the bottom edge of the panel there is a button to remove existing codes. The right panel, much bigger, has a series of frames (the number depends on the number of predefined languages) with a floppy disk icon and a “Delete” button to the left of each frame. Each frame must have the corresponding translation into the language whose name is displayed to the left of the floppy disk icon. On the top edge of this panel there are two controls: “Available languages” and “Generate file” for the functions suggested by their names.

So, to enter a New Multi-language Code and its corresponding texts in the multiple languages that the Program admits we should proceed as follows: To start with, we click the “+” button or take an existing one as a base, and then we modify it by clicking the button with the “copy” icon, we enter the new text or modify the one existing in the text box located just below the “Multi-language codes list”, we enter the text translated into the corresponding language in frame on the right of the language selected and then we click the button with the Save (floppy disk) icon. We repeat the same process for all the languages that we want to translate the text into (predetermined languages in the Program) saving each time the changes made. Once the process of inputting the different translations is finished, we must click the “Update System” button in order to make the modifications effective in the whole computer system.

**Temporal events**

Both in the Laboratory and in the Ultrasound Units, modifications in the reagents or in the equipment used to assess the different markers may occur. In the laboratory, for example, the autoanalyzers are recalibrated, new lots of reagents are received or new ultrasound scanners are bought. In these cases, SsdwLab6 should be informed about which modification, and when, has taken place. This information should be reflected in the different quality controls that assess the screening (CUSUM, MoM Median). This is the objective of this section.

It displays two submenus, one for Laboratory Events and one for Ultrasound Units events.
Laboratory Temporal Events

This submenu allows you to register the temporal events that may affect the assessments of the biochemical markers performed by the Biochemistry Laboratory, such as the calibration of the autoanalyzers, change of reagent lots, etc. In the CUSUM and MoM Median quality controls we can choose an option which displays the data of two previously registered events (Begin Event and End Event).

It provides the following options: Add (a new event) and Edit or Delete (a previously registered event), and allows you to register the event’s Start date, the Laboratory (if there are more than one) as well as the Description of the event and the possibility of writing Comments on it. Save and Cancel perform the functions that their names suggest.

Ultrasound Units Temporal Events

This submenu allows you to register the temporal events that may affect the assessments of the ultrasound markers performed by the Ultrasound Units, such as the calibration of the different ultrasound scanners, the replacement of a scanner, etc. In the CUSUM and MoM Median quality controls we can choose an option which displays the data of two previously registered events (Begin Event and End Event).

It provides the following options: Add (a new event) and Edit or Delete (a previously registered event), and allows you to register the event’s Start date, the Ultrasound Unit (if there are more than one) as well as the Description of the event and the possibility of writing Comments on it. Save and Cancel perform the functions that their names suggest.

Traceability Menu

This is a menu which contains the options specifically designed to monitor all the actions performed by the Program as well as the access and actions carried out by all its users. It has two submenus: History Consultation, Log Consultation and User Statistics.
Historic Search

To obtain the traceability of any operation related to the screening, whenever a user edits, creates or deletes a patient’s data, SsdwLab6 stores in a historic table detailed information about the user, the operation carried out and the parameters used.

The history screen provides access to the history table in the database and offers a series of filters which allow filtering easily according to a particular user, a specific action, or a particular patient.

This screen is divided into 3 sub-panels, 1 on the left that contains the possible selectable filters, and 2 on the right, one at the top in grid or table format with the list of all the filtered histories, and one at the bottom that displays in XML format all the parameters received by the operation when it is run.

**Historic table fields:**

- idHistoric: Historic identifier.
- dtHistoric: Date of the operation.
- coUser: User who performs the action.
- neAction: Type of operation (EDIT, NEW, DELETE).
- neClass: Structure it affects (in English): Patient, Pregnancy, ScreeningReq, Gestation, UltraSound, BloodTest, screeningCalc, IT, MUS, Birth.
- saKey: Structure identification parameters.
- binObject (selected item): Date sent by the user at the time of carrying out the operation.

**saKey Field**

This field is a text string that contains all necessary data to identify a structure (neClass) with the following format:

> [patientid / pregnancy id / screening id / fetus id/ specific structureid]

Examples:

neClass = Patient ->saKey = [idPatient]
neClass = Gestation -> saKey = [idPatient, idPregnancy, idScreening]
neClass = ScreeningCalc -> saKey = [idPatient, idPregnancy, idScreening, idFetus]
neClass = Birth -> saKey = [idPatient, idPregnancy, idScreening, idFetus, idBirth]

**binObject Field (Selected Item)**

In the database, the `binObject` field keeps in binary format all the parameters used in the operation made by the user.

At the top of the screen, this information is displayed coded in XML, which makes it easy to consult by the administrator.

Example of patient editing operation:

```xml
    <idPatient>271</idPatient>
    <idPregnancy>1</idPregnancy>
    <dtCreation>2009-07-25T00:00:00Z</dtCreation>
    <dtUpdate>2009-07-31T00:00:00Z</dtUpdate>
    <coUserUpdate/>
    <dtLMPRef>2009-07-25T00:00:00Z</dtLMPRef>
    <saObstetricFormula/>
    <blEggDonation>false</blEggDonation>
    <ndDonatorAge>0</ndDonatorAge>
    <nePregnancyType>1</nePregnancyType>
    <nuFetusNumber>1</nuFetusNumber>
    <btMonoDichorial>2</btMonoDichorial>
    <ndMaternalWeight>60</ndMaternalWeight>
    <nuMaternalHeight>0</nuMaternalHeight>
    <ndMaternalBMI>0</ndMaternalBMI>
    <btPreviousT21>0</btPreviousT21>
    <btPreviousT18>0</btPreviousT18>
    <btPreviousNTD>0</btPreviousNTD>
    <nuCigarrettesDay>0</nuCigarrettesDay>
    <btFolicAcid>0</btFolicAcid>
    <nuAgePaternal>0</nuAgePaternal>
    <coCountryPaternal/>
    <coRacePaternal/>
    <coEthnicGroupPaternal/>
</ifPregnancy>
```

**Log Consultation**

The logs are used to trace the activity taking place in the program, locate possible incidences or for complete monitoring of a specific user or patient.

The logs screen allows querying the log table.
This screen is divided into 2 sub-panels, 1 on the left with the possible selectable filters, and one on the right in grid or table format which displays the list of all the filtered logs.

**Log table fields:**
- idLog: Log identifier.
- dtLog: Date of the operation.
- coUser: User who performs the action.
- saHostAddress: User's IP.
- saCall: Call made.
- saExtra: Identification parameters of the call.
- nuResult: Operation status.
- swResultText: Operation status report.

**Differences between logs and historics**
- Logs store only the identification parameters used in the operation. (Historics store all the parameters)
- Logs store information from all the operations carried out in the program. (Historics store the operations concerning the patient’s data and screenings).
- Logs store the operation status. (OK, warning, Error)
- Logs store the IP address of the user's computer.

**Interpretation of results:**
- Status: (black→ OK, yellow→ Warning, red→ Error).
- Id _User code _IP | Opera tion (Parameters) | date.

**Use of filters:**
- Typeof Error: Operation status.
- IP, User: IP, User code.
- saCall: Call made.
- saExtra: Identification parameters of call. (To monitor the operations performed on a patient, the patient’s id must be entered in this field).

Help menu

This menu has the options specifically designed for the presentation of Help in PDF format (SsdwLab6 User Guide) and About Ssdwlab6.

SsdwLab6 User Guide

This option displays all the documentation available about the Software, with the table of contents on the left side of the screen and the descriptions and images on the right side. This same complete documentation is also available in the directory where the Software was installed, in PDF format and in the different languages.

About SsdwLab6

This screen shows the identity features of the SsdwLab6 Software.
Running the Program
Security mechanisms for results

In the presence of errors or absence of data

SsdwLab6 implements a wide range of security mechanisms to prevent the output of incorrect results when the information entered into the program contains mistakes or when the program does not contain all the necessary data to perform risk calculations.

The program automatically corrects certain typing errors or displays on-screen dialog boxes (messages that force the user to carry out a certain action) reporting the type of error present. This occurs when the Program suspects or proves that an error has been made in data input or in the calculation process, record saving, printing, import-export of information, violation of access rights, etc. If the error persists or compromises the result of the risk calculations, the results are not displayed or printed.

In addition, the program checks all the values that must be entered between a certain intervals before their acceptance. If any values are incorrect, a message appears, as in the case of maternal weight, height and age, fetal CRL, gestational age, etc.

The input of any date, entered by means of a calendar or keyed in directly, begins a process to verify that the date is really possible. If dates later than the current day are entered, a warning message is shown. Also, whenever numeric intervals or intervals between dates are selected, the Program checks that the second is greater than the first.

Whenever incorrect data are entered or information required for risk calculations is missing, the Program deletes from the screen any information relating to automated calculations, such as gestational age or risk indices and these do not appear again until the information is correct or complete. Also, when the print command is pressed for a report with incorrect data, the program displays a message to indicate that the data is probably incorrect; the risk calculations do not appear.

The following more general procedures, have been implemented to minimize the risks of program errors caused by user action:
Gestational age. Gestational age may be estimated in four ways: LMP (Last Menstrual Period), Biometry, Ultrasound, or Conception Date. When the program has enough information, the gestational age at screening date, in weeks and days and in total days, will be displayed in the automated calculation frame. Once the means of determining the time of gestation has been selected, the program automatically calculates the gestational age at the time of screening and establishes the expected delivery date. If the gestational age is outside of the established limits for the screening profile in use, the program does not calculate the MoMs and therefore the risk cannot be estimated. The gestational age at the time of screening is also specified in the report.

Creating a Screening. Creating a new screening profile is a task exclusively reserved for the program administrator, who should have wide epidemiological knowledge and experience with program handling. Once a profile has been used, it is no longer possible to modify its basic parameters (Lock); this prevents conflicting results due to the application of different profiles for the same patient. To validate the effectiveness of a certain profile, the program allows the direct input of markers such as MoM, which makes it possible to compare the results with those of other profiles. The program also has an online calculation option to find out the percentage of positive results using a certain profile, which gives us an idea of the effectiveness of given profiles.

Modifying the screening profile. Only program users with the Administrator User Profile with all the privileges can modify the profile. The profile name also appears on the written report given to the doctor and the patient.

Biometry charts. Fetal biometry charts are used for two purposes: 1 - to estimate the gestational age at the time of screening (in this case the result appears in the automated calculation frame) and 2 - for the MoM calculation of the ultrasound markers, such as NT. The program uses different biometry charts published by distinguished authors. Each centre can use its own charts but only an Administrator with all the privileges can modify them. If the value of the biometry used is outside of the limits established for the curves, a pop-up window will appear, notifying the user that the value entered is not correct; in this case, the risk is not calculated.

Previous trisomy 21 affected fetus. This is highlighted using bold typeface in the report for the doctor and the patient.

Marker value. The extreme values of the biochemical markers should be truncated to allow an acceptable calculation of the likelihood ratio. When the value entered is outside the truncation limits, a message box asks the user to confirm that the value is correct. Once confirmed, the program allows the calculations to be carried out. When the values of the different markers are saved, the MoM (corrected and uncorrected) are calculated and displayed on
the screen, which allows verifying the correction of the calculations made.

Reports generated by the program. Because the report is generated automatically and cannot be amended by the final user, errors can only appear if programming errors are present. This possibility has been ruled out due to the level and specificity of the tests carried out.

To avoid errors caused by external factors, it is highly advisable to take the following general precautions (which are universal for all software):

Electrical power supply interruption. The computer must have a UPS installed. It is also vital to make backup copies.

Viruses. The computer used to run the program should be protected by up-to-date antivirus software.
Final Notes

Warning

The program authors, producers and distributors of the SsdwLab6 do not accept responsibility for the decisions derived from using this computer application with regard to each individual patient or groups of patients.

Licence

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Use of all the functions of the program on a single computer, or on a computer network, under the conditions that are detailed in this "EULA".

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The End-User will be responsible for the knowledge and fulfillment of the laws, effective in his Country, relating to security measures for automated files that contain data of a personal nature, and of rights concerning the patient's health, autonomy and clinical documentation.

Intellectual Property and Distribution Rights

All the intellectual property rights are reserved for the authors of the Program. SBP SOFT 2007 SL has the distribution rights for the SsdwLab6 program. The distribution of copies of the Program and its documentation for any technical system is completely forbidden, unless the purpose is to create backup copies or for the information of the personnel attributed to a screening service that has a License for use (granted by the Program proprietors or their legally authorized representatives).

Production, distribution, information and maintenance

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English Translation

Francesc Planells Ribas
Glossary of Terms

**Button**
Command that allows the execution of the action indicated by its text.

**Check Box**
Control that allows the entry of Boolean type information (Non Assessed/False/Not and True/Yes) and in some cases: Non Assessed (grey check box with check mark that takes the value of "2"), False or Not (white check box that takes the value of "0") and True or Yes (check box with white background and check mark that takes the value of "1").

**Combo Box**
Data input box that drops down a list, with the possible or accepted values, when the inverted triangle to its right is pressed. Depending on the associate database field it allows the entry of non-concordant values with those from the presented list.

**Command (button)**
Button that allows the execution of the action indicated by its text.

**Control**
All elements of a form that allow the display and/or entry of information, or the execution of an action.

**Database**
Data group related to a topic or certain purpose. A database contains tables and can also contain queries and indexes, as well as relationships between tables, fields and tables' validation criteria and links to external sources of data.

**Field**
Information category stored in a database table; a data column. A component of a database table that contains a specific element of information, such as surname.
Folder
Secondary form that displays the information, and the controls, located in different planes. Access to each plane is through the tabs, like the folder of a filing cabinet.

Form
Window or dialog panel. The forms are containers of controls.

Frame
Rectangular area that contains a group of related controls and/or information.

Grid or table
Means of visually displaying a data Table, with the fields in columns and the records in rows, which allows navigation through the different fields and records by means of horizontal and vertical scroll bars.

HASP HL Key
Hardware protection system against unauthorized use and copying of the SsdwlLab6 program, consisting of a key connected to one of the computer’s USB ports, and which is needed to run the Program.

Label
Graphic control not accessible to the user, which is used to describe the function or contents of the controls dedicated to information input. It is usually located to the left of the control that it describes.

List Box
Data box that displays a list of fixed values from which a selection can be made, in certain cases of more than one.

Menu Bar
A bar, located at the top of the main form, from which different menus of the Program can be deployed.

Option Button
Group of more than one button of which only one can be active at one time.

Record
Group of related columns or fields containing data. A row is like a record in the Microsoft Jet database engine.

Status Bar
Information bar located at the bottom of the main form.
**Table**
Basic unit of data storage in a relational database. A table stores data in records (rows) and fields (columns) and it usually contains a specific category of things, for example, patients. Also-called base tables.

**Text Box**
Data input box. For some fields, the type, correction and width of the values is verified during input or when abandoning it.

**Toolbar**
Group of buttons or commands, grouped and situated below the Menu Bar.

**Tool Tip Text**
Floating label that contains information relating to a certain control and which becomes visible when the mouse pointer is located above this control.